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The ReCell spray-on skin system for treating skin loss, scarring and depigmentation after burn injury: medical technology consultation document

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The ReCell Spray-On Skin system for treating skin loss, scarring and depigmentation after burn injury

The National Institute for Health and Care Excellence (NICE) is producing guidance on using the ReCell Spray-On Skin system for treating skin loss, scarring and depigmentation after burn injury in the NHS in England. The Medical Technologies Advisory Committee has considered the evidence submitted and the views of expert advisers.

This document has been prepared for public consultation. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the public. This document should be read along with the evidence base (see Sources of evidence considered by the Committee).

The Advisory Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical effectiveness and resource savings reasonable interpretations of the evidence?
- Are the provisional recommendations sound, and a suitable basis for guidance to the NHS?
- Are there any equality issues that need special consideration and are not covered in the medical technology consultation document?

Note that this document is not NICE's final guidance on the ReCell Spray-On Skin system for treating skin loss, scarring and depigmentation after burn injury. The recommendations in section 1 may change after consultation. After consultation the Committee will meet again to consider the evidence, this document and comments from public consultation. After considering these comments, the Committee will prepare its final recommendations which will be the basis for NICE's guidance on the use of the technology in the NHS in England.

For further details, see the [Medical Technologies Evaluation Programme process guide](#) and [Medical Technologies Evaluation Programme methods guide](#).

Key dates:

- Closing time and date for comments: 19 May 2014
- Second Medical Technologies Advisory Committee meeting: 17 July 2014

NICE medical technologies guidance addresses specific technologies notified to NICE by sponsors. The 'case for adoption' is based on the claimed advantages of introducing the specific technology compared with current management of the condition. This case is reviewed against the evidence submitted and expert advice. The medical technology guidance on the ReCell Spray-On Skin system for treating skin loss, scarring and depigmentation after burn injury recommends further research. This recommendation is not intended to preclude the use of the technology in the NHS but to identify further evidence which, after evaluation, could support a recommendation for wider adoption.

1 Provisional recommendations

1.1 The ReCell Spray-On Skin system shows potential to improve healing in acute burns. However there is insufficient evidence on its use in clinical practice, particularly in relation to which patients might benefit most from its use, to support the case for its routine adoption in the NHS.

1.2 Research is recommended to address uncertainties about the claimed patient and system benefits of the ReCell Spray-On Skin system. The research should include time to 95% healing, length of hospital stay, cosmetic appearance of the scar and function of the burned area, compared against standard care. The research might include analysis of data generated from existing databases and registers. NICE will explore the development of appropriate further evidence, in collaboration with the technology sponsor and with clinical and academic partners, and will review this guidance when new and substantive evidence becomes available.

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2 The technology

Description of the technology

2.1 The ReCell Spray-On Skin system (Avita Medical; 'ReCell') is a rapid, autologous cell harvesting, processing and delivery system for treating skin loss and preventing scarring and depigmentation in adults and children with burns. The ReCell Spray-On Skin is prepared by shaving a 0.15–0.20 mm thick piece of skin, measuring up to 2 cm by 2 cm, from a donor site close to the burn. The donor skin is added to a proprietary enzyme solution (derived from pigs) in a processing unit and heated for 15–30 minutes to disaggregate the cells. The skin is then removed and scraped with a scalpel to develop a plume of cells. These cells are added to a buffer solution, aspirated and filtered to create a cell suspension that contains keratinocytes, melanocytes, fibroblasts and Langerhans cells. The suspension is delivered to the debrided burn using a spray applicator, or it can be dripped directly onto the site. Cells from the suspension are able to proliferate rapidly and migrate in the wound bed. The regenerative nature of these skin cells is intended to promote the growth of healthy skin to achieve rapid healing. The procedure is designed to be carried out by clinicians, without input from specialised laboratory staff.

2.2 ReCell is supplied as a sterile pack containing all the components needed to create and apply a skin cell suspension sufficient to treat burn injuries up to 320 cm². The cost of ReCell is given as £950 plus VAT per pack.

2.3 The claimed benefits of ReCell in the case for adoption presented by the sponsor are:

- Shorter wound healing time at the recipient site, leading to:
- reduced frequency of dressing changes to weekly rather than daily allowing earlier discharge and outpatient management, thus reducing length of stay in hospital
- reduced need for dressing changes under anaesthetic
- fewer complications and reduced morbidity
- improved aesthetic results for burn wounds, with a lower likelihood of scarring
- reduced likelihood of later readmission for corrective surgery as a result of improved aesthetic results.
- Repopulation of melanocytes to reduce hypopigmentation and improve skin colour match in healed wounds.
- A reduction in skin graft donor site size and depth.
- Shorter healing time at the donor site.
- A reduction in the need for external technical laboratory support.

Current management

2.4 The treatment of burns can be considered in 2 phases: acute and reconstructive. The acute phase is the initial management of the burn wound, with the aim of healing with minimal scarring and physical limitation. The reconstructive phase aims to improve the functional or visual effect of scarring, usually by surgical means, and may be done months or years after the initial injury.

2.5 The first step in managing a burn injury is to assess the proportion of the body surface area involved, the burn depth, and the site of the burn. The extent of a burn is usually expressed as a proportion of the total body surface area affected. Burn depth is classified according to the layer of skin (epidermis, dermis or subcutaneous layer) affected. Burns can be classified as:

- epidermal or superficial, affecting the epidermis only, as in cases of sunburn
- partial thickness or dermal, affecting the dermis and stratified into superficial, mid-dermal or deep
- full thickness, where the epidermis, dermis and subcutaneous layer, and in some cases the underlying muscle

or bone, are affected.

2.6 Superficial epidermal burns and full thickness burns are easily identifiable by experienced clinicians, but burn depth can be more difficult to assess accurately in partial-thickness burns, and in children because they have thin skin. Burn depth is usually assessed by clinical evaluation using visual and tactile assessment. NICE recommends the use of the [moorLDI2 Burns Imager: a laser doppler blood flow imager for burn wound assessment](#) (NICE medical technology guidance 2) to assess burn depth when this is uncertain. Burns can be of mixed depths within a single injury site and can be dynamic, becoming deeper over time, depending on the cause and initial treatment. Burns of uncertain depth are often classed as indeterminate or intermediate.

2.7 Epidermal and superficial partial thickness burns tend to heal without scarring or surgical intervention within 21 days. Mid-dermal or deep partial thickness burns and full thickness burns may need surgical excision or debridement to remove the burnt skin and tissues. It is usual for surgical excision to be done within 48 hours of admission. The burn wounds are then dressed with conventional or biosynthetic dressings, or skin grafts in more serious burns. Skin grafting is used to promote rapid healing, to minimise scarring and to reduce complications. Healing can occur only from the edges of a burn wound, so without a skin graft the wound can contract. This contraction and formation of scar tissue can lead to a poor cosmetic outcome and reduced mobility. Skin grafting is often used to treat mid-dermal or deep partial thickness burns. For mixed-depth burns, or if there is uncertainty over depth, a decision about whether to use skin grafting is based on assessment of burn healing and the patient's condition, between 10 and 21 days after the injury. Delayed healing (more than 21 days) increases the probability of hypertrophic scarring. Full thickness burns more than 1 cm in diameter will always need skin grafting because the regenerative components of the skin have been lost.

2.8 Skin grafts may be classified as partial or full thickness grafts, depending on how much of the dermis is harvested by the surgeon. The clinical 'gold standard' for skin grafting is an autologous (from the patient's own skin) split-thickness graft taken from an area of unburnt skin. Grafts should ideally be taken from donor sites adjacent to the injury to improve the match with the surrounding skin. However, the size and location of the burn injury can limit the choice of donor site, so grafts may be taken from other areas of the body. The donor site is itself a wound and needs treatment to ensure healing. If large grafts are needed for extensive burns, the donated skin can be perforated (or meshed) to increase its surface area. The mesh ratio differs depending on the area needing coverage and is generally between 1:1.5 and 1:4 times the original skin size. The pattern of meshing can be visible after healing, so sheet (non-meshed) grafting is preferable for a good cosmetic result.

2.9 Alternatives to autologous skin grafts for deep partial thickness and extensive full thickness burns include bio-engineered skin substitutes, which may be cultured autologous skin cells (epithelial autografts), synthetic dermal substitutes and artificial membranes. Cultured epithelial autografts need cells (usually keratinocytes) from a donor site to be grown in vitro either as sheets or in a liquid suspension. Culturing can take days or weeks and cells are then applied directly or can be attached to synthetic or biological carriers such as silicone, collagen or fibrin glue. Cultured skin cells can also be used in conjunction with other dermal substitutes or autologous grafts in full thickness injuries.

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3 Clinical evidence

Summary of clinical evidence

3.1 Full details of all clinical outcomes considered by the Committee are available in the [assessment report overview](#).

3.2 The key clinical outcomes for the ReCell Spray-On Skin system ('ReCell') presented in the decision problem were:

- speed of healing
- length of stay
- degree of scarring
- degree of pigmentation
- device-related adverse events.

3.3 The sponsor presented 11 studies: 3 peer-reviewed articles (Gravante et al. 2007, Park et al. 2013 and Wood et al. 2012) and 8 conference abstracts. An abstract by Sen et al. (2012) reported findings from a case series which overlapped with a study by Philp et al. (2013), submitted as academic in confidence. The External Assessment Centre considered 2 of the conference abstracts (Echlin 2012b and Palombo 2012) to be outside the decision problem because these studies evaluated the treatment of donor site wounds and hypertrophic scars rather than acute burns. The External Assessment Centre identified a further 9 conference abstracts, of which 2 were unavailable (Rawlins 2010 and 2011b) and 5 contained data that overlapped with references presented by the sponsor.

3.4 The sponsor also presented 5 additional published studies in support of the degree of pigmentation, which was an outcome included in the decision problem. The External Assessment Centre considered these studies to be outside the scope because they evaluated treatments for people with vitiligo or hypertrophic scars and not with burns.

Studies included in the sponsor's submission

3.5 Gravante et al. (2007) compared ReCell against skin grafting for treating deep partial thickness burns. Time to complete epithelialisation, pain, aesthetic and functional scar quality and procedure time were assessed in 82 adults. Time to complete epithelialisation was 13 ± 2 days for the ReCell group and 12 ± 2 days for the skin grafting group (difference not statistically significant). Postoperative pain in the ReCell group was statistically significantly lower than pain in the skin grafting group (3.3 ± 1.6 in the ReCell group compared with 6.8 ± 1.2 in the skin grafting group, $p=0.03$). Postoperative analgesia levels were the same in both groups, although patients in the skin grafting group 'complained of an additional painful site (the area of harvesting)'. The total donor site in the ReCell group was statistically significantly smaller than that in the skin grafting group ($p<0.001$). Aesthetic scar quality was measured using the Vancouver scar scale and the development of contractures after 1 month was also measured as an indication of function in the burned area. Quantitative Vancouver scar scale values were not reported but were described as not different between the groups according to the judgment of 2 plastic surgeons. In the ReCell Spray-On Skin system group, 12 patients (29%) developed at least 1 contracture, as did 15 patients (38%) in the skin grafting group (difference not statistically significant). Procedure time was significantly longer for the ReCell group than for the skin grafting group (59 ± 4 minutes [mean \pm standard deviation] for ReCell and 20 ± 6 minutes for grafting, $p<0.001$). A second procedure was needed for 7 patients (17%) in the ReCell group and 6 (15%) in the comparator group.

3.6 Park et al. (2013) compared outcomes for 722 patients who were admitted to an Australian burns centre between January 2004 and December 2011 and who needed skin grafting or a skin replacement procedure. A total of 770 patients were enrolled in the study but 48 were later excluded from this analysis. The authors reported that 724 enrolled patients were divided into 3 groups: ReCell alone ($n=73$), ReCell plus standard skin graft ($n=264$), or standard skin graft alone ($n=387$): it is assumed that 2 of these patients were later excluded but no information was reported as to their treatment group. The study reported that the type of surgical intervention did not influence the likelihood of the patient having a burn wound infection. ReCell alone was associated with a shorter hospital stay than standard skin grafting alone (actual values not reported, odds ratio 0.7, 95% confidence interval [CI] 0.57 to 0.82, $p<0.01$) but ReCell plus standard skin grafting was not associated with a shorter hospital stay (odds ratio 0.98, 95% CI 0.88 to 1.10, $p=0.85$). The authors concluded that patients treated with ReCell alone had a 30% shorter length of hospital stay ($p<0.01$) compared with standard skin grafting. The External Assessment Centre questioned the validity of the statistical analysis, but noted that the authors stated that the shorter hospital stay observed in those treated with ReCell alone should be interpreted carefully because wound depth and surgery timing differed between the ReCell and standard skin grafting groups. The study authors also speculated that the reduction in donor skin harvesting associated with the ReCell technique may have reduced the length of hospital stay.

3.7 Wood et al. (2012) evaluated the use of ReCell plus a biosynthetic dressing (Biobrane), Biobrane alone, and standard treatment (dressings every 2–3 days with definitive surgery at 10–14 days after the injury) in 13 children followed up over 6 months. At 10 days after the initial burn, none of the patients in the ReCell plus Biobrane group were assessed as needing surgery; 1 patient in the Biobrane group needed surgery, and 3 out of 4 patients in the standard treatment group needed surgery. The median time to complete healing for ReCell group was similar to the time for the Biobrane group and the median time was longer in the standard treatment group (median [interquartile range] 16.0 [11.5–18.0], 16.0 [14.25–23.0] and 36.5 [18.5–47.7] days respectively; no statistical analysis provided). The patients treated with ReCell plus Biobrane had a higher proportion of wound area healing at both 10 and 21 days after the burn compared against Biobrane alone or against standard treatment (no statistical analysis provided).

3.8 Dunne and Rawlins (2012a) observed 40 children in the UK who were treated either by ReCell plus Biobrane (mid and deep dermal burns, $n=13$), or Biobrane (superficial dermal burns, $n=20$), or standard skin grafting (full thickness burns, $n=7$). The authors reported that hospital stay was shorter and scar assessment was better in the ReCell plus Biobrane and the Biobrane groups, although neither numbers nor statistical significance were reported. The External Assessment Centre noted that this was a non-comparative review of treatments in burns of different depths and could be considered as 3 separate case series.

3.9 Echlin et al. (2012a) observed 5 patients with mid to deep dermal facial burns (3 scalds and 2 flame burns) in the UK. Four patients were treated with ReCell plus non-adherent dressings because they were assessed 9–11 days after the burn and their burns were deemed unlikely to heal within 3 weeks. One further patient was assessed 23 days after injury and was treated with ReCell plus an allograft. The authors concluded that ReCell increased the speed of wound healing (mean 5 days for those treated 9–11 days after the burn, maximum healing time 7 days) and decreased the rate of standard skin grafting and subsequent scar formation, but no comparative data or statistical analyses were reported. The authors reported that as a result of this study the burns service involved (Chelsea and Westminster) changed its practice to treat these wounds with ReCell rather than a skin graft.

- 3.10 Rawlins et al. (2011a) compared the outcomes for 15 adults with deep dermal flame burns treated 48–72 hours after injury with either ReCell plus Biobrane (n=5), or standard skin grafting (n=10). The mean time to wound healing (no healing measurement defined) was 18 days in the ReCell plus Biobrane group and 48 days for the standard skin grafting group. No statistical analyses were reported. The authors reported that less analgesia was needed in the ReCell plus Biobrane group than in the standard skin graft group and that scar quality was better in the ReCell plus Biobrane group, but values were not reported.
- 3.11 Rawlins (2013) described the outcomes for 26 children with deep dermal burns who were treated with ReCell (n=11) or a standard skin graft (n=15). The mean visual analogue scale score for scar quality, assessed by independent clinicians, was very similar in the 2 groups (3.9, 95% CI 2.8 to 4.9 for ReCell and 3.9, 95% CI 3.3 to 4.5 for standard skin graft; p=0.97). Operative time was longer for ReCell than for standard skin grafting (mean 87 minutes compared with 58 minutes; p=0.05), although the total burn surface area was greater for the ReCell group than the standard skin graft group (mean total burn surface area of 6.5% compared with 2.9%; p=0.04).
- 3.12 Sen et al. (2012) reported data from a case series which overlaps with a study by Philp et al. (2013), a report on which was available to the Committee as academic in confidence data. Sen et al. reported narrative findings from a case series of 5 patients with deep partial or full thickness burns over more than 50% of their total body surface area. Burns were covered with split thickness skin grafts and split thickness dermal grafts. The split thickness dermal grafts and donor sites were treated with ReCell. The graft and donor sites were assessed by 2 independent observers. Graft take was reported as being complete for all patients and healing was reported to be similar to that for patients treated with skin grafting alone.

Additional studies identified by the External Assessment Centre

- 3.13 Dunne and Rawlins (2012b) reported early results from the same study as Rawlins (2013).
- 3.14 Dunne and Rawlins (2013) reported outcomes for 11 children treated with ReCell plus Biobrane for scalds and 10 adults, 8 of whom were treated with ReCell plus Biobrane for flame burns. The nature of the burns in the other 2 adults was unclear, as was the treatment they received. This was a retrospective review with possible overlap with Rawlins (2011a, 2013), Rawlins et al (2011a and 2011b) and Dunne and Rawlins (2012b). Wound coverage, pigmentation, hypertrophic scarring and donor site morbidity were assessed. One child needed a standard skin graft after treatment with ReCell but early wound coverage and good pigmentation were reported with minimal hypertrophic scarring or donor site morbidity.
- 3.15 Hiller et al. (2013) (possible overlap with Rennekampff et al. 2011, see section 3.17) described the outcomes for 5 patients who had partial thickness facial burns and who were treated with ReCell. Only narrative outcomes were reported, with the authors reporting accelerated healing time and an improvement in scar quality.
- 3.16 Rawlins (2011a) and Rawlins et al. (2011b) (overlap with Rawlins et al. 2011a, see section 3.10) described outcomes for 4 patients treated with ReCell plus Biobrane compared with 10 matched controls who received standard skin grafts. Time to healing (healing measurement not defined) was 18 days in the ReCell plus Biobrane group and 48 days in the standard skin grafting group. Analgesia needs and length of hospital stay were reported as being reduced in the ReCell group compared with standard skin grafting, but no statistical analyses were reported. After 6 months, an assessment using the Vancouver scar scale demonstrated better scar outcomes in the ReCell group (5.3) than in the standard skin graft group (6.5).
- 3.17 Rennekampff et al. (2011) (possible overlap with Hiller et al. 2013, see section 3.16) reported outcomes in a case series of 5 patients with facial burns who were treated with ReCell. The depth of the burns was not clearly reported, although the authors' discussion implied that partial and full thickness burns were included. The authors reported that the full thickness burns needed skin grafting, however they did not state clearly that these burns were also treated with ReCell. Time to epithelialisation was reported as being 7–9 days after surgery and skin pigmentation was described as being slightly reduced compared with skin surrounding the area. No hypertrophic scars or severe contractions occurred.
- 3.18 Sood et al. (2009) reported findings from an intra-patient comparative study in 10 patients with partial thickness burns. Each patient was treated with ReCell in 1 area and meshed skin grafting in another. Skin graft 'take' (not clearly defined) was the main outcome reported. Results showed the overall graft take was 93.6% at the ReCell sites and 98.2% at the standard skin graft sites. Eight patients had 100% graft take in the ReCell group and 9 in the standard skin grafting group.
- 3.19 The External Assessment Centre identified 1 ongoing multicentre randomised, within-patient controlled feasibility study that fitted the decision problem but no findings were available.

Additional work requested by the Committee

- 3.20 The Committee requested additional information on the potential effect of the use of ReCell on improving skin colour match in burn scars. The External Assessment Centre gathered this information from an additional literature search and a survey of clinical experts, in conjunction with further work requested by the Committee in revising the sponsor's cost modelling (see sections 5.7–5.9).
- 3.21 The External Assessment Centre identified 3 comparative studies examining the effect of using ReCell on the repigmentation of stable vitiligo lesions.

- 3.22 Daniel et al. (2011) reported interim results in a conference abstract from an intra-patient randomised comparison of ReCell compared against mini-grafting in 14 patients with stable vitiligo. Repigmentation at 3 months was 27% for the ReCell-treated areas compared with 11% for mini-grafting, but at 12 months the proportions were 15% and 12% respectively (not statistically tested).
- 3.23 Venugopal et al. (2009) reported results in a conference abstract from an intra-patient randomised comparison of ReCell compared with mini-grafting in 12 patients with stable vitiligo who completed a 6-month follow-up. Pigmentation results were 'highly variable' with no difference between treatments, although ReCell produced a more uniform repigmentation in some cases.
- 3.24 Mulekar et al. (2007) conducted an intra-patient comparison of ReCell against melanocyte-keratinocyte transplantation in 5 patients with stable vitiligo. At 4 months postoperatively results were comparable, with 100% repigmentation in both sites in 2 patients, no repigmentation in either site in 1 patient, 65% for ReCell compared against 100% for melanocyte-keratinocyte transplantation in 1 patient and 40% for ReCell compared against 30% for melanocyte-keratinocyte transplantation in 1 patient.
- 3.25 The External Assessment Centre stated that results from the comparative studies were inconclusive. The clinical experts surveyed by the External Assessment Centre pointed out that there were physiological differences between burns and surgically created wounds, such as debrided vitiligo lesions prepared for treatment. The opinions of the experts about whether outcomes from the treatment of vitiligo could be transferable to burns were divided, but most experts stated that they might consider using ReCell for acute burns if it could be shown to have benefit in hypopigmentation conditions.

Adverse events

- 3.26 No adverse event reports relating to ReCell were found in a search of the Manufacturer and User Facility Device Experience (MAUDE) database operated by the US Food and Drug Administration.

Committee considerations

- 3.27 The Committee heard clinical expert advice that a key motive for using ReCell would be to reduce burn healing time, which could reduce the risk of infection and the degree of scarring, as well as shortening length of hospital stay. It also noted the potential benefits associated with using ReCell for treating burns by generating viable skin cells from a small donor site. However, the Committee judged that there was insufficient evidence to quantify any improvements in burn healing time, reduction in length of stay and improvements in pigmentation in healed burns to make a recommendation for adoption.
- 3.28 The Committee heard expert advice that small (up to 10% total body surface area) partial thickness burns usually heal with conventional dressings or a biosynthetic dressing such as Biobrane, without the use of skin grafting. The Committee considered the clinical evidence taken together with the clinical expert advice gathered by the External Assessment Centre (see sections 5.7–5.9). It accepted the conclusions from the External Assessment Centre's survey of clinical experts, in which the majority agreed that these burns would heal without the use of skin substitutes. The Committee concluded that ReCell was unlikely to be beneficial in treating patients with small partial thickness burns.
- 3.29 The Committee noted that the available clinical evidence suggested that ReCell may be an effective alternative to skin grafting for mid-dermal to deep dermal partial thickness burns and the need for a smaller donor site may offer advantages. The Committee was aware that most of these studies were carried out outside the UK. However, the Committee was advised that current clinical opinion would not favour the use of ReCell as an alternative to skin grafting in these burns in NHS practice.
- 3.30 The Committee heard clinical expert advice that ReCell might be used alone on mid to deep dermal or indeterminate depth burns where the need for grafting is initially unclear. The External Assessment Centre confirmed that there was some support for this scenario in its survey of expert clinical opinion (see section 5.15). The Committee concluded that ReCell may offer some benefit in this group from avoiding skin grafting and better scar outcomes, but that further evidence about these outcomes would be needed.
- 3.31 The Committee was advised by experts that the patients most likely to benefit from the use of ReCell were those with large full thickness or deep partial thickness burns that need meshed skin grafting. It was advised that potential applications include the use of ReCell on skin graft donor sites to reduce healing time and allow further grafts to be taken sooner from the same site to treat very large burns. The Committee was aware that there was little published evidence on these outcomes and requested further information. The Committee considered additional clinical expert advice subsequently gathered by the External Assessment Centre and concluded that use of ReCell in conjunction with meshed skin grafts in these burns and donor sites showed promise, but the evidence was inconclusive.
- 3.32 The Committee considered the possibility that ReCell might reduce the occurrence of hypopigmentation in healed burns, as a result of the retention of melanocytes in the cell suspension. It noted that scar skin colour match was an important consideration for burns patients, but that primary evidence for pigmentation outcomes when using ReCell in burns was scarce. At its first meeting, the Committee noted a difference in clinical expert opinion on the relevance of data on using ReCell for treating hypertrophic scars or for non-burn indications such

as vitiligo. It therefore asked the External Assessment Centre to include questions about skin colour match in burns scars in its additional work, as well as reviewing any relevant evidence. The Committee accepted the External Assessment Centre's conclusion from their additional work that both the study evidence and expert opinion on pigmentation outcomes when using ReCell are inconclusive.

3.33 The Committee judged that further evidence should be gathered from additional research to investigate the clinical utility of using ReCell in:

- full thickness or deep partial thickness burns that need sheet or meshed grafting (see section 3.31) and
- partial thickness or indeterminate depth burns where the need for grafting is unclear (see section 3.30).

The Committee was advised that observational data, such as those collected in the International Burn Injury Database or from well-designed clinical audit, could be useful in helping to resolve some of the clinical uncertainties in these patient groups.

3.34 For larger burns needing wide-meshed skin grafting, the Committee heard advice from clinical experts that cultured cells are sometimes used in the NHS to promote healing. Their advice concurred with the findings in the External Assessment Centre's additional report, that the choice of whether to use cultured cells or ReCell was based on the availability of cultured cells and the personal preferences of clinicians, and not on any good comparative evidence. The Committee was advised by clinical experts that using cultured cells has the advantage of the availability of large volumes of viable cells, but may be associated with a fragile epithelium and problems with skin loss in the healed burn. The External Assessment Centre confirmed that there was currently no evidence comparing ReCell against cultured cells. The Committee concluded that data from further research comparing these treatments would be useful.

3.35 The Committee was advised by clinical experts that multicentre research into the effectiveness of ReCell in treating burns would be possible, but difficult, particularly for large full-thickness burns that occur in only a small number of people each year. The Committee was also advised that it might be hard to determine the effect of the use of ReCell or other treatment strategies on length of hospital stay because many other factors influence this in patients with large, deep burns. Careful selection of patients would be necessary to minimise the confounding effect of comorbidities.

3.36 The Committee heard expert clinical advice that time to 95% healing is a standard measure and would be a useful endpoint to include in any research, in addition to length of hospital stay, cosmetic appearance of scars (assessed using a validated scale) and a measure of function in the burned area.

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4 NHS considerations

System impact

4.1 The claimed system benefits in the case for adoption presented by the sponsor are that the ReCell Spray-On Skin system ('ReCell') may lead to a reduction in:

- length of stay in hospital because weekly rather than daily dressing changes are needed, allowing earlier discharge and outpatient management
- need for re-dressings under anaesthetic.

Committee considerations

4.2 The Committee was advised by clinical experts that in large full or deep partial thickness burns, length of stay in hospital is influenced by many factors in addition to wound healing time. These factors include other injuries sustained at the time of the burn such as inhalation injuries, existing comorbidities and psychosocial factors. The Committee concluded that further research would be necessary in a carefully selected group of patients to determine the effect of using ReCell on length of hospital stay, because the resource implications were unclear.

4.3 The Committee accepted the findings from the External Assessment Centre's report that there was considerable variation in practice in the frequency of dressing changes. The Committee considered that evidence about the possible effect of using ReCell on the number of dressings used could be gathered in further research.

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5 Cost considerations

Cost evidence

Published evidence

5.1 The External Assessment Centre excluded all the studies identified by the sponsor because they were outside the scope, although it did recognise that the studies contained useful cost information for standard care. The External Assessment Centre initially considered that the study by Wood et al. (2012) (not presented by the sponsor as part of its economic evidence) may provide some relevant evidence on costs but after quality assessment, which showed several limitations (small number of patients, non-UK care pathway, heterogeneous population), the External Assessment Centre concluded that the evidence could not be generalised to support the sponsor's economic case.

Sponsor's cost model

5.2 The sponsor submitted a de novo cost analysis comparing the ReCell Spray-On Skin system ('ReCell') plus conventional dressings, ReCell plus Biobrane, Biobrane alone, and conventional dressings alone, for treatment of a partial thickness 640 cm² burn. Full details of all cost evidence and modelling considered by the Committee are available in the [assessment report overview](#).

5.3 The sponsor submitted a base case analysis modelling patients treated for partial thickness burns including scalds, for which mesh grafting was not needed. Patients needing a meshed skin graft were not included in the model. The model covered a 21-day period with the first 10 days observing whether wounds had 100% epithelialisation (completely healed) or incomplete healing. Other clinical parameters in the model included length of time as an inpatient and need for a skin graft.

5.4 In the base case, the sponsor assumed a time to healing of 15 days (based on the mean time to 100% epithelialisation) for the conventional dressing treatment arm. This was based on the median from 3 studies observing conventional topical burn treatments (Caruso et al. 2006; Cuttle et al. 2007; Silverstein et al. 2011). The sponsor then used a percentage reduction in healing time for the conventional dressings to calculate healing times for the other 3 interventions. The estimated reductions were based on results from Wood et al. (2012) and Echlin (2012b) and were 30% for Biobrane or ReCell alone and 40% for the combination. The estimates of the number of people who were treated as inpatients were based on clinical opinion obtained by the sponsor. The proportion of patients having a standard skin graft was based on clinical studies (Caruso et al. 2006; Cuttle et al. 2007; Ostlie et al. 2012; Silverstein et al. 2011) which may have overestimated the proportion because of the patient populations included. Clinical opinion also suggested this figure may be lower (5–10%). The sponsor used clinical opinion to inform this parameter for the other interventions.

5.5 The sponsor's base case included several key assumptions:

- A burn size of 640 cm² (5–10% total body surface area depending on the age and size of the patient).
- The burn was considered to be partial thickness with no definite areas of deep involvement.
- Burns were considered sufficiently severe to warrant initial debridement in theatre. Patients having conventional and Biobrane treatment were assumed to need 20 minutes theatre time at the start of treatment, whereas those treated with ReCell would need 30 minutes theatre time (based on clinical opinion).
- All patients would remain as inpatients until day 2. Those who were discharged at this point would receive re-dressing either as outpatients or as ambulant visitors to the ward (based on clinical opinion).
- All patients were assumed to have their burn managed on a general burns ward (or in an outpatient clinic if discharged). The sponsor excluded intensive care unit costs because it considered these costs would obscure other treatment cost differences.

5.6 The sponsor explored the uncertainty around the model parameters and the effect this had on the incremental cost of ReCell using a one-way sensitivity analysis. The results of the sensitivity analysis showed that in all of the scenarios presented, ReCell was cost saving compared with conventional dressings, except for the smaller wound size of 320 cm², when ReCell and ReCell plus Biobrane were more costly than conventional dressings. In all of the other scenarios Biobrane was the lowest cost option followed by ReCell plus Biobrane, ReCell alone and conventional dressings.

5.7 After reviewing the available economic evidence, the Committee asked for information on the cost consequences of using ReCell to treat full or deep partial thickness burns in conjunction with grafting, in the form of a revised economic model (see section 5.18). The Committee also requested further information on 3 parameters used in the sponsor's existing model for partial thickness burns not needing grafting that it considered to be particularly uncertain, which were length of hospital stay, time to epithelialisation and need for a skin graft. The External Assessment Centre carried out additional work to gather information from clinical experts working in NHS burns units and centres to inform revisions to the model.

5.8 The External Assessment Centre was asked to consider full or deep partial thickness burns in 2 subgroups:

- Full or deep partial thickness burns judged to need skin grafting, likely to need 1 round of surgery with inpatient stay on a general ward only. The interventions for this group were skin grafting in conjunction with ReCell and ReCell alone. The comparator was skin grafting alone.
- Large area full or deep partial thickness burns judged to need wide meshed skin grafting, likely to need multiple

rounds of surgery and grafting and time in an intensive care or high dependency unit. The intervention for this group was meshed grafting with ReCell and ReCell alone at the donor site. The comparator was meshed skin grafting alone and standard donor site treatment.

The External Assessment Centre further classified these 2 groups as including burns covering 10% and 40% of the total body surface area respectively, based on referral thresholds to burns services. The External Assessment Centre intended to use these parameters as the base case for the model and to vary them in sensitivity analyses. It also classified the partial thickness burns not needing grafting as those covering 10% of the total body surface area for the purposes of gathering information about the uncertainties in the sponsor's model. Adults and children were considered separately within the burn groups.

5.9 In order to find further information to inform the analysis of full or deep partial thickness burns in the 2 subgroups, the External Assessment Centre carried out an initial literature search around burn care in the UK. Results from this search, the sponsor's model and previously identified literature were used to create a list of parameters for which information was needed. The External Assessment Centre devised a questionnaire to gather data on these parameters, with the help of the lead clinical experts from the evaluation. The questionnaire was aimed at capturing quantitative information for the revised modelling and also for the 3 uncertain parameters from the sponsor's model. It also included questions to gather qualitative data on the cosmetic outcomes of using ReCell in burns and vitiligo. The questionnaire was administered as a semi-structured interview with optional email follow-up because of the volume of questions included and the opportunity to gain additional insight from the clinicians.

5.10 The External Assessment Centre tried to obtain data from the International and National Burn Injury Databases (iBID and NBID) but was unable to gain access within the timeframe for the additional work.

5.11 The External Assessment Centre contacted lead clinicians from all specialist burns units and centres identified in England and Wales (adult and paediatric; 18 in total). Interviews were conducted with 10 clinicians, 9 consultant burns surgeons and 1 specialist burns nurse. Another burns surgeon provided comments on a summary of the data. Three of those interviewed had not used ReCell but all respondents were familiar with it.

5.12 The data collected for each of the 3 groups are summarised in tables 5–7 of the [External Assessment Centre's additional report](#) (pages 14–17). For the 10% total body surface area partial thickness burns not needing grafting, the External Assessment Centre found that many adults would be treated with conventional dressings rather than Biobrane and would not be taken to an operating theatre. Children would be more likely to be treated with Biobrane, which would need a general anaesthetic in an operating theatre. The External Assessment Centre found some variation between sites in terms of the care pathway and little quantitative data. Most respondents indicated that this type of burn would usually heal within 2 weeks without the need for alternative treatments such as ReCell. Those using ReCell in this group indicated that it would need additional theatre time and could not provide any quantifiable data about reduced healing time, subsequent need for grafting or scar outcome.

5.13 For the 10% total body surface area full or partial thickness burns needing grafting, the External Assessment Centre found that unmeshed sheet rather than meshed skin grafting was more likely to be used. Most respondents indicated that ReCell would not be used alone or with Biobrane in patients who were treated with sheet skin grafts.

5.14 For the 40% total body surface area full or partial thickness burns likely to need meshed grafting, the External Assessment Centre found considerable variation in practice between sites. Available data from the International Burn Injury Database indicated that there would be around 8 or 9 patients treated in each burns centre each year making generalisable estimates of the treatment pathway difficult. Many respondents described using autologous cultured cells in conjunction with meshed skin grafts to improve the speed of healing and to improve the appearance of the healed burn. Autologous cultured cells are available from 1 NHS laboratory and 1 commercial provider and take around 2 weeks to produce. ReCell was generally considered for use when cultured cells were not available. The respondents expected healing time to decrease and cosmetic outcome to improve with the addition of autologous cells but were unable to provide quantitative data.

5.15 The External Assessment Centre asked all interviewees what they considered the role of ReCell in treating acute burns to be. All interviewees were open to the possibility that ReCell might have some benefit, particularly in large burns needing skin grafting. The immediate availability of cells produced using ReCell was considered to be an advantage over the use of cultured cells needing a 2-week wait; however, some clinicians expressed a preference for cultured cells as a result of available volume and cell viability. Another advantage of ReCell identified was its use with left-over pieces of donor skin from grafting, which would otherwise be discarded. However, the External Assessment Centre noted that this may extend theatre time. The respondents identified 2 other options for the use of ReCell. In mid-dermal, mixed depth, intermediate or indeterminate burns ReCell could be used with the hope of reducing healing time and the need for later skin grafting. The other option identified was its use in deep facial burns as an additional treatment when the burn had not healed well after 2 weeks.

5.16 The External Assessment Centre summarised the available evidence from the assessment report, the additional literature search and the expert survey for 9 main parameters in section 3.3 of its additional report (pages 18–23).

5.17 The External Assessment Centre stated that the lack of quantitative data for the clinical benefits or resource

impact of using ReCell meant that it was unable to produce revised economic modelling for burns needing skin grafting. The External Assessment Centre concluded that the uncertainties in the parameters used in the sponsor's model (length of hospital stay, time to healing and proportion of patients needing skin grafts) could not be verified. The findings from the expert survey indicated that ReCell was unlikely to be used to treat this type of burn in the NHS because these burns usually heal without the need for skin substitutes and so there would be no benefit from its use.

Committee considerations

5.18 The Committee noted that the sponsor's economic model did not include the treatment of large area full or deep partial thickness burns needing skin grafting, as identified in the decision problem for the evaluation. The Committee heard expert clinical advice that the use of ReCell in this patient group might have substantial clinical benefits. Therefore, the Committee asked the External Assessment Centre to produce economic analysis for the treatment of these burns to aid its decision-making in developing recommendations for ReCell. The Committee was aware of the lack of published data for this patient group but it considered that parameters for the economic analysis could reasonably be obtained by expert opinion from a broad range of clinicians working across NHS burns units and centres. The Committee also suggested that hospital-based audit data might be available to inform the model.

5.19 The Committee was unconvinced about the validity of some of the assumptions in the sponsor's model for partial thickness burns – in particular the length of hospital stay, time to healing and the proportion of patients needing skin grafts. The Committee accepted the conclusions of the External Assessment Centre's additional work that several parameters in the sponsor's model for smaller partial thickness burns not needing grafting could not be validated (see section 5.17). It also accepted the advice that ReCell is unlikely to be used by clinicians in the NHS for this group of patients because their burns would usually be treated with conventional or biosynthetic dressings without skin substitutes.

5.20 The Committee considered the External Assessment Centre's conclusion that there were insufficient data to revise the cost modelling to include the use of ReCell in full or deep partial thickness burns needing grafting. The Committee queried the effect of potential reductions in healing time on length of hospital stay for these burns in the NHS. In the light of expert clinical advice that treating these burn injuries has a high cost to the NHS and that a reduced stay could have a relatively large effect on resource use, the Committee considered that further research on use of ReCell should include evaluation of its cost and resource impact.

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6 Conclusions

6.1 The Committee concluded that the ReCell Spray-On Skin system ('ReCell') is a promising technology with potential to improve healing in acute burns, especially for patients with burns that need skin grafting. However, the Committee judged that there was insufficient evidence about the most appropriate patient population and, therefore, the clinical and cost benefits of using ReCell to support the case for routine adoption at the present time.

6.2 The Committee decided that further research into clinical outcomes of using ReCell for treating burns would be beneficial. It considered that further research could determine the benefits of treatment with ReCell in patients with larger full thickness or deep partial thickness burns, or mid-dermal partial thickness or indeterminate depth burns. The Committee considered that evidence about the relative benefits and costs of ReCell compared against cultured cells in treating large burns in combination with meshed skin grafts would be useful in making decisions about the use of ReCell for these patients.

6.3 The Committee concluded that research could reasonably involve the use of data from existing sources such as the International Burn Injury Database, as a supplement to other methods. The Committee considered that time to 95% healing, length of hospital stay, cosmetic appearance of scars and a measure of function of the burned area would be important outcomes in any research or data analysis.

Bruce Campbell

Chairman, Medical Technologies Advisory Committee

April 2014

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7 Committee members and NICE lead team

Medical Technologies Advisory Committee members

The Medical Technologies Advisory Committee is a standing advisory committee of NICE. A list of the Committee members who took part in the discussions for this guidance appears below.

Committee members are asked to declare any interests in the technology to be evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each Medical Technologies Advisory Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

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NICE lead team

Each medical technology assessment is assigned a lead team of a NICE technical analyst and technical adviser, 2 clinical expert advisers, a patient expert (where appropriate), a non-expert member of the Medical Technologies Advisory Committee and representative of the External Assessment Centre.

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Technical Analyst

Bernice Dillon

Technical Adviser

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Lead Expert Advisers

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Non-Expert MTAC Member

Sue Peirce and Grace Carolan-Rees

External Assessment Centre Representatives

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8 Sources of evidence considered by the Committee

The External Assessment Centre report for this assessment was prepared by Cedar:

- Peirce S, Carolan-Rees G. The ReCell Spray-On Skin system for treating skin loss, scarring and depigmentation after burn injury, October 2013. Cedar

Submissions from the following sponsors:

- Avita Medical Ltd. (manufacturer)
- JB Medical Ltd. (sponsor)

The following individuals gave their expert personal view on the ReCell Spray-On Skin system by providing their expert comments on the draft scope and assessment report.

- Miss Isabel Jones, ratified by the British Association of Plastic, Reconstructive and Aesthetic Surgeons - clinical expert
- Dr Rebecca Martin, nominated by the Association of Burns and Reconstructive Anaesthetists - clinical expert
- Dr Sarah Pape, ratified by the British Association of Plastic, Reconstructive and Aesthetic Surgeons - clinical expert
- Mr Bruce Philp, ratified by the British Burn Association - clinical expert
- Dr Amber Young, nominated by the Association of Burns and Reconstructive Anaesthetists - clinical expert

The following individuals gave their expert personal view on the ReCell Spray-On Skin system in writing by completing a patient questionnaire or expert adviser questionnaire provided to the Committee.

- Miss Isabel Jones, ratified by the British Association of Plastic, Reconstructive and Aesthetic Surgeons - clinical expert
- Dr Rebecca Martin, nominated by the Association of Burns and Reconstructive Anaesthetists - clinical expert
- Dr Sarah Pape, ratified by the British Association of Plastic, Reconstructive and Aesthetic Surgeons - clinical expert
- Mr Bruce Philp, ratified by the British Burn Association - clinical expert
- Dr Amber Young, nominated by the Association of Burns and Reconstructive Anaesthetists - clinical expert

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Cedar

Healthcare Technology Research Centre

ReCell Spray-on Skin System

Additional Report following MTAC meeting of November 2013

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Version: 1.1



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Executive Summary

The primary purpose of this project was to obtain data from suitable expert advisers to answer MTAC questions prior to its recommendations on ReCell. The objectives were as follows:

- To confirm using expert advice or any relevant data whether the model parameters (length of in-patient stay, time to epithelialisation and requirement for a skin graft) have been accurately estimated in the sponsor’s submission.
- To carry out an economic analysis of the cost impact of the ReCell Spray-On Skin System for treating burns which require grafting. This was to be considered as two subgroups:
 - ◇ Large area burns which are judged to need wide mesh grafting
 - ◇ Full thickness or deep partial thickness burns which are judged to need skin grafting
- To collect information from experts group and analyse responses about use of ReCell Spray-on skin to improve skin colour match in scars.

The EAC collected data from 10 UK expert advisers (9 consultant burn surgeons and 1 burns nurse consultant) from specialist Burn Units and Centres in England and Wales using semi-structured interviews. This report presents the collected expert adviser data. This provides useful information regarding the NHS treatment pathways for patients who are in need of treatment at this level of specialised burn service. The EAC has summarised the available evidence for the use of ReCell in these patient populations collected from the previous assessment report, additional literature review and the survey of expert advisers conducted here.

However, the participants were unable to provide quantitative data suitable for use in the economic models as they either thought that the use of ReCell conferred no clinical benefit or resource savings or they could not provide any numerical estimates to support its assessment. Therefore no new economic modelling was possible. The EAC:

- Found no difference in length of in-patient stay, time to epithelialisation and requirement for a skin graft between ReCell and comparators for partial thickness burns where mesh grafting is not required. This does not validate the sponsor model parameters.
- Was unable to carry out an economic analysis of the cost impact of the ReCell Spray-On Skin System for treating burns which require grafting
- Found no evidence to support the claim that the application of ReCell results in systematically improved long term scar outcomes, including pigmentation



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1 Introduction

1.1 Rationale for this project

The ReCell spray-on skin system is the subject of a NICE MTEP evaluation. Following the sponsor’s submission and External Assessment Centre’s (EAC) assessment report, MTAC considered that insufficient economic modelling had been conducted by the sponsor and that further modelling was required. The aim of this additional work was to obtain data from UK burns surgeons and other sources (such as audits or registries) for the following:

- To confirm using expert advice or any relevant data whether the model parameters (length of in-patient stay, time to epithelialisation and requirement for a skin graft) have been accurately estimated in the sponsor’s submission.
- To carry out an economic analysis of the cost impact of the ReCell Spray-On Skin System for treating burns which require grafting. This was to be considered as two subgroups:
 - ◇ Large area burns which are judged to need wide mesh grafting
 - ◇ Full thickness or deep partial thickness burns which are judged to need skin grafting
- To collect information from experts group and analyse responses about use of ReCell Spray-on skin to improve skin colour match in scars.

The EAC was therefore asked to identify suitable experts, collect the data and conduct economic modelling for the use of ReCell in 3 populations of patients:

	Population	Intervention	Comparators
Group A	Partial thickness burns where mesh grafting is not required	ReCell alone ReCell plus biosynthetic dressing	Conventional dressings Biosynthetic dressings
Group B	Full thickness or deep partial thickness burns which are judged to need skin grafting	ReCell alone ReCell plus skin graft	Skin graft alone
Group C	Large area burns which are judged to need wide mesh grafting	Skin mesh graft in combination with ReCell and possible use of ReCell at donor site.	Skin mesh graft and current donor site treatment. Consider use of cultured cells with skin mesh graft.

Group A was modelled in the sponsor’s submission. The EAC was asked to determine whether the parameters used in this model were accurately estimated and to revise and re-run the model as appropriate. Groups B and C required new economic models to be designed and executed by the EAC.

2 Methods

2.1 Initial study design

The original design of the project was to use three information sources for the data with which to define, populate and run the 3 economic models:

- data from the International/National Burn Injury Database (iBID, NBID, Section 2.2),
- additional data from a literature search for supplementation or validation (Section 2.3), and
- a survey of burn surgeons working in Burn Centres and Units across England and Wales to provide quantitative data about actual practice (Section 2.4).

2.2 International Burn Injury Database (iBID)

iBID is co-ordinated from Wythenshawe Hospital in Manchester and collects data from specialist burn services around the UK. Data from this is combined with other data sources (Hospital Episode Statistics and National Burn Bed Bureau) to create the National Burn Injury Database. It contains data from 2003 onwards and information about the iBID database fields indicated that it contained data about dressing changes, treatment types and outcomes as well as epidemiology (Evolution Healthcare Systems).

Access to this resource was requested by the EAC as quickly as possible following the start of the project. However, the iBID team were unable to provide us with access to the data within our timeframe. We determined that the database and data entry software had undergone a redesign in 2012/2013 and were also advised that some of the apparently relevant fields may have been added recently and therefore would not contain a large amount of data. Although this resource was therefore unavailable for this MTEP project it may be of use in future research in burn care technologies.

2.3 Literature search

An initial scoping literature search was conducted to identify published information regarding current UK clinical practice and suitable parameters (resource use, costs and outcomes) for use in the economic models. The search strategy combined 'burns' (focused MeSH heading) with a series of keywords designed to limit the results to UK-based authors or institutions. It was conducted in Medline and Embase only and restricted to papers published since 2000. This search returned approximately 1500 results, which were searched by keywords to identify key papers that described aspect of standard care, economics, length of stay, healing times, use of cells or skin substitutes or other suitable candidate parameters. Information from these papers assisted with early development of both the model structures and the expert survey.

Medline, NHS EED and HEED were searched specifically for economic evidence on burns care. This search was intended to provide additional information regarding potential model parameters and to validate and supplement that obtained from the clinical experts. The strategy used to search Medline is provided in Table 1 (searched on 13-01-14). Of the 346 papers identified, 37 were

selected for further scrutiny based on title and abstract. NHS EED (searched on 08-01-14) and HEED databases (searched on 29-01-14) were searched using the terms ‘burn’ or ‘scald’. NHS EED produced 40 results, of which 21 were selected for further scrutiny. HEED did not return any additional papers.

Table 1: Economic literature search strategy (Medline)

1	exp Burns/	18725
2	scald.mp.	908
3	exp "Costs and Cost Analysis"/	114621
4	econom*.mp.	125996
5	1 or 2	18886
6	3 or 4	213823
7	5 and 6	346

2.3.1 Main literature search

It was intended that following the issuing of the quantitative survey a targeted search strategy would be developed to identify published data in which outcomes and resource use data relevant to the economic model were reported. A few such papers had been identified during the work for the ReCell assessment report, but that search had primarily targeted literature that reported ReCell as an intervention. In this new search we would primarily look for data relevant to the comparators in the economic models; standard care, biosynthetic dressings and cultured cells. Any data identified in this way would be used to validate and supplement that obtained from the clinical experts.

As the data collection for the survey progressed it became apparent that there would be insufficient quantitative data on ReCell to populate the ReCell arm of the economic model (see below). As there was no new data for the ReCell intervention this systematic literature searching would only provide additional data for the comparators therefore this literature search did not proceed.

2.3.2 ReCell literature search

The EAC conducted an additional literature search for papers involving ReCell that included data from outside the scope of the original assessment report. This was done in order to identify any potential benefits of the technology that may be relevant to its use in burn care. In the assessment report literature search all relevant papers that reported ReCell had included its brand name. Also the use of alternative descriptors for the technology (e.g. ‘spray’, ‘suspension’, ‘cells’) produced more than 25,000 results. Therefore the search strategy adopted by the EAC for this work consisted solely of the keyword ‘ReCell’. This was applied in Medline, Medline in progress, Embase, Web of Science, Scopus and the Cochrane Library databases.

2.4 Survey of Burn Surgeons

2.4.1 Expert advisers

Specialist Burns Centres and Units in England and Wales were identified from the NHS Specialised Services website (NHS Specialised Services). Burn Facilities were not included as these treat the more minor burn categories and would not treat the large area burns included in Group C; they were also excluded from the original scope. There are around 18 unique sites for Burn Centres and Units including adults and paediatric burn services. The exact number depends the defined entity (hospital

site or NHS Trust) and also some services are split across more than one hospital. Geographically close services may also be listed separately but actually share staff and common practices.

An individual consultant at each service was identified using a combination of Trust websites, regional Burn Care Networks and the membership of the national Burn Care Clinical Reference Group (NHS England). Each consultant was invited to participate by email or to nominate another consultant from their department. Initial invitations were followed up with further emails and telephone calls for around 2 weeks until 15 participants had been recruited. Additionally, a senior specialist burns nurse was invited to participate. Participants were not screened for their experience with ReCell as we wanted a representative selection of current standard care as well as direct experience with ReCell. We assumed that a sufficiently broad and large sample of participants would provide a range of experience levels and a general indication of the level of use of ReCell in the UK NHS. Participants were also self-selecting to a certain extent, as initial contacts who were unwilling to participate sometimes passed the invitation onto their colleagues. Previous experience with clinical experts indicated that a primary selection criteria should be willingness to participate rather than identification of ideal candidates who may decline.

2.4.2 Questionnaire design

The purpose of the survey was to elicit information with which to populate the economic models for the 3 patient populations. This entailed 2 distinct types of question:

- 1) Where are the potential differences in pathway, costs, resource use and outcomes when ReCell is used, compared to standard care?
- 2) What is the estimated size of those differences?

In the sponsor’s submission their economic model included four parameters in which ReCell was thought to provide a resource saving:

- the proportion of patients treated as inpatients
- the difference between (full) conventional dressing changes and secondary dressing changes
- the proportion of patients requiring a skin graft at around 2 weeks post-treatment
- time to healing of the burn wound.

However, this model did not address most of the sponsor’s claims as described in the scope, nor did it include other potential benefits and detriments identified in the published literature. The EAC used information from the scoping literature search and the work done during the ReCell assessment report to identify potential model parameters for question 1 above:

Table 2: Potential resource use and outcome parameters

Source	Parameter
Sponsor’s model	Need for inpatient treatment
Sponsor’s model, Wood et al. (2012)	Need for skin (re)graft
Sponsor claims	Graft donor size and depth
Sponsor’s claims, sponsor’s model	Donor site complications & healing time
Sponsor’s claims	Burn wound healing time
Sponsor’s claims	Aesthetic outcome, scarring, skin colour
Sponsor’s claims	Hypopigmentation
Sponsor’s claims	Dressing change frequency

Wood et al. (2012)	Number of dressing changes
Sponsor's claims	Need for GA during dressing changes
Sponsor's claims, Park et al. (2013)	Length of hospital stay
Sponsor's claims	Need for external laboratory support
Sponsor's claims	Need for later corrective surgery
Gravante et al. (2007), Wood et al. (2012), Rawlins et al. (2011)	Pain and analgesia
Gravante et al. (2007), Rawlins (2013)	Surgical procedure time
Rawlins (2013)	Duration of physiotherapy
Sponsor's model, Wasiak et al. (2013)	Dressing type/cost
Sponsor's model, Wasiak et al. (2013)	Nursing time

The MTEP lead team expert advisers were consulted about the patient pathway for standard care. These multiple sources provided the basis for the assumed patient pathway and the economic model and questionnaire design. The questions were developed collaboratively and iteratively, with EAC colleagues involved in brainstorming and discussion. We designed the survey in parallel with the initial development of the three economic models to ensure that the questions centred on collecting the data required. A generic patient pathway flowchart was designed to encapsulate the assumptions and options for treatment of patients admitted to a specialist burns service (see below) and this was sent to the participants as a visual aid alongside the questionnaire.

We considered a 2-part survey that would address questions 1 and 2 separately. This would have the advantage of only collecting detailed data about parameters that had been confirmed as significant. However due to the short timescale of this project and the difficulty of getting multiple rapid responses from participants we decided to collect all potentially relevant data in a single questionnaire. The main drawback of this approach was the increased length and complexity of the survey as it involved asking detailed information about all potentially important parameters. We included detailed questions about resource use alongside questions about clinical practice and outcomes. For example, we postulated that use of ReCell increases surgical procedure time (based on Gravante et al. 2007 and Rawlins 2013) and therefore included questions about staff and other resources included in typical burns surgery; this was needed to estimate any effect on costs. An example questionnaire is included in Appendix 1.

We further defined the patient populations as follows (TBSA – total burn surface area):

- Groups A and B – 10% TBSA
- Group C – 40% TBSA

The sponsor's submission defined the initial Group A as a burn area of 640 cm², which they stated as equivalent to approximately 5-10% TBSA. The EAC considered this equivalent to about 3.5% TBSA for an adult and 10-15% TBSA for a small child (Sacco et al, 2010; Sharkey et al. 2001). As the burns community traditionally uses TBSA as their measure of injury extent the EAC used this as the means to define the patient populations. The referral thresholds are between 2-10% TBSA for Burn Units and 20-40% TBSA for Burn Centres. Therefore a sensitivity range of 5-15% TBSA was considered to be appropriate for burns that would not require wide meshing of autografts, but would still require referral to this level of service. This was consistent with the sponsor's original model. A size of 40% TBSA was determined as suitable for Group C, as around 30-40% TBSA was suggested as the lower

limit at which wider meshing of autografts would be required due to paucity of donor sites. It was thought that there was effectively no upper limit to TBSA for this patient population.

The TBSA sizes were intended to serve as the base case scenarios for the economic modelling, allowing for a variation of $\pm 5\%$ TBSA in Groups A and B and $\pm 10\%$ TBSA in Group C in the sensitivity analysis.

This level of information covering three patient populations and multiple treatment options resulted in the questionnaire becoming a long document and the EAC considered that it would be complex for participants to complete by themselves. It was thought that significant differences between the care of adult and paediatric patients would require separate answers. Additionally there was the risk of misunderstanding of both questions and answers and that variations in local practice may not be consistent with the assumptions inherent in the questionnaire design. We therefore determined that conducting telephone interviews with participants using the questionnaire as a basis would be more effective and efficient and would enable misunderstandings to be clarified immediately. Participants were therefore offered the choice of completing the questionnaire themselves, being interviewed or a combination of the two methods.

SP conducted the interviews, which were digitally recorded and the recordings and handwritten notes used to complete the questionnaire. These were sent to the individual participants for review. The data from multiple participants was anonymised and summarised into tables for the 3 patient populations and these were sent to all participants to allow them to comment on the appropriateness of the data.

2.4.3 Patient pathway and questionnaire assumptions

The generic patient pathway was determined using the sponsor's submission, work conducted during the assessment report, the lead team expert advisers and the scoping literature search (Appendix 2). Explicit assumptions were provided in the questionnaire for each patient population and interviewees were asked to comment on their appropriateness. A description for each population group excluded injuries on complex anatomical or cosmetically important sites as these were likely to involve special consideration for treatment options. They also excluded patients with other injuries or co-factors so that clinical outcomes and resource use would be based on the skin burn wounds alone.

2.4.4 Economic modelling

Early development work for the economic modelling involved brainstorming and group discussion work in parallel with the questionnaire design. Clinical pathways and model designs were iteratively and collaboratively produced using information from the assessment report work, scoping literature review and lead team expert advisers. It was expected that the new model designs for patient Groups B and C would be substantially different to that produced in the sponsor's submission. This was due to the criticisms of the model identified in the assessment report and because the model failed to address many of the sponsor's claimed benefits and potential detriments listed in Table 2. It was also expected that it would be relatively simple to adapt the new models to account for Group A patients. It was therefore intended that the EAC would create a new model for this patient population as well as re-populating and running the sponsor's model.

The questionnaire was intended to identify *where* realisable differences in costs and outcomes existed between ReCell and comparator treatments as well as their estimated *magnitude*. Therefore the final designs for the economic models were to be completed using results from the survey. However, as interviews for the questionnaire proceeded it became clear that experts were not able to provide support for any generalisable benefits or resource savings resulting from the use of ReCell in the three identified patient populations (Section 3.2). As such, there was no data to inform the final model designs or to populate the intervention arms. No new economic models were created for patient Groups B and C.

3 Results

3.1 Literature search

3.1.1 Scoping search

Around 150 papers from the scoping literature search were identified as potentially useful in identifying standard UK clinical practice or suitable parameters for the economic models. However, no new parameters were identified from this literature in addition to those listed in Table 2.

Most of the economic evaluations identified by the search strategy consisted of comparisons of different dressings or other topical treatments or were related to burn prevention strategies. Only one UK economic evaluation paper on burns was identified that could potentially provide data on NHS resource use and costs for standard care treatment of burns (Phillips et al. 2011). There were no economic evaluations involving ReCell in burns. As the EAC did not proceed with the economic modelling the information identified was not used.

3.1.2 Additional ReCell papers

A total of 54 papers were retrieved from the literature search using the keyword 'ReCell'. This included studies examined during the assessment report work and some that were excluded at that point as out of scope. Three comparative studies were identified that examined the effect of ReCell in the repigmentation of stable vitiligo lesions. No comparative studies in donor sites were identified.

Daniel et al. (2011) is a conference abstract reporting interim results from an intra-patient randomised comparison of ReCell versus mini-grafting in 14 patients with stable vitiligo. Percentage repigmentation at 3 months was 27% for ReCell-treated areas versus 11% for mini-grafting, but at 12 months the proportions were 15% and 12% respectively (not statistically tested). Qualitative assessment of the donor site was better for ReCell but "most subjects preferred the speckled pigmentation at recipient sites of the mini-grafting".

Venugopal et al. (2009) is a conference abstract reporting results from an intra-patient randomised comparison of ReCell versus mini-grafting in 12 patients with stable vitiligo who completed a 6 month follow-up. Percentage pigmentation results were 'highly variable' with no difference between treatments, although ReCell produced a more uniform repigmentation when it worked. Patients reported more post-operative pain of the ReCell donor site than the mini-grafting site.

Mulekar et al. (2007) conducted an intra-patient comparison of ReCell versus melanocyte-keratinocyte transplantation (MKT) in five patients with stable vitiligo. At 4 months post-operatively results were comparable with 100% repigmentation in both sites in 2 patients, no repigmentation in either site in 1 patient, 65% versus 100% and 40% versus 30% repigmentation (ReCell versus MKT) in the remaining two patients.

Other papers retrieved were case studies and non-comparative studies or case series. Additionally one interviewee referred to a study using a method similar to ReCell. Back et al. (2009) is a randomised intra-patient comparison of autologous melanocyte-keratinocyte spray versus placebo spray (suspension medium) in 13 patients with vitiligo. There was no difference in the time to epithelialisation (median of 7 days) between treatment and placebo. Normal pigmentation was achieved in 5 out of 13 patients at 1 or more time points, but at 12 months follow-up 11 out of 13 patients had no pigmentation in the treated area. Additionally 2 patients developed normal pigmentation temporarily on areas treated with the placebo solution. Repigmentation was described as ‘unpredictable’ and ‘infrequently persistent’.

The EAC has not conducted a systematic review or critically appraised these papers. This summary is provided as background to the question of whether ReCell affects pigmentation outcomes in acute burns and whether data from *repigmentation* studies could be extrapolated to outcomes in burns (Section 3.4). Overall, these studies indicate that the use of ReCell can produce repigmentation in stable vitiligo, but that outcomes are highly variable, comparable to other treatments and that early positive results may deteriorate.

3.2 Expert survey

3.2.1 Participants

Initially 14 surgeons and 1 specialist burns nurse agreed to participate. Due to the length of the questionnaire several of these were unable to complete the interviews in the timescale available. Interviews were conducted with 10 individual expert advisers (9 consultant surgeons and 1 specialist burns nurse) and an additional participant provided commentary on the summary data (Appendix 3). These individuals represent a mixture of Burn Centres and Units for both adults and paediatric patients as shown in Table 3. Note that NHS Trusts can provide burns services for either or both patient groups, at the same or different levels and that one Trust may provide both services at the same or separate hospital sites. Staff may also work across hospital sites.

Table 3: Sites participating in the survey

	Adult	Paediatric
Centre	3	5
Unit	4	4

3.2.2 ReCell experience of the participants

Three of the 10 interviewees had no personal experience of using ReCell. The others varied from semi-regular current users to those who had used it a few times several years previously. All participants indicated familiarity with the technology and with published evidence regarding it. None indicated that they had been involved in any formal or semi-formal studies or evaluations of ReCell.



Table 4: Summary of interviewees' ReCell experience

1	Used semi-routinely over last 3-4 years.
2	Involved in use ~6 times a couple of years ago. Personal use on animal models.
3	Used some time ago.
4	Used ~12 times.
5	Used up to ~10 times.
6	Used during training in Australia, ~10 cases in UK.
7	Used during training in Australia.
8	No personal experience. Seen it used on several patients by colleagues.
9	No personal experience. Seen evidence.
10	No personal experience. Seen it demonstrated.

Interviewees were asked which of the treatment options was used by them for each patient population. Data presented in this report represents the personal experience of the interviewees or their observations of colleagues. Interviewees were not asked to speculate about resource use or outcomes in treatments or patient groups in which they were not experienced. For example, paediatric Burn Units do not treat patients in the Group C population as these would be transferred to the appropriate Burn Centre.

3.2.3 Nature of the data collected

By interviewing participants, their responses were commonly quite discursive. They provided additional information in response to a single question and talked about other patient groups (e.g. 'In a 5% burn I would...'). Conducting the interviews was a balance between the breadth of information wanted, the detail that interviewees went into, the precision/vagueness of their responses and the duration of the interview. Also, as the interviews progressed it became apparent that some information was very consistent (e.g. healing time for donor sites) and that some questions were essentially unnecessary (e.g. the repetition of questions about long term outcomes and data sources at the end of each patient group). The data collection method is best described as semi-structured interviews. Full coverage of the questions was not achieved, although where information was missing or ambiguous following transcription, interviewees were asked to complete the data or clarify their responses by email. Interviewees were given the opportunity to review their transcribed questionnaires and to compare their responses with those provided by other (anonymised) interviewees.

One interviewee mentioned internal audit data – the EAC requested this but it was not provided during the timescale of the project. In addition, length of stay is used as a key performance indicator with a target of 1 day/% TBSA for non-elderly patients, so interviewees tended to use this as an estimation method where they did not recall a value. However, in most cases it was difficult for respondents to provide quantitative values and the data reported here often represents their best guess. In some cases they were unable or reluctant to provide estimates for some parameters. There was also occasional ambiguity with the definition of the parameters (e.g. theatre time or time to healing). Both of these factors will have contributed to the apparent variance in the data, but some is the result of real differences in practice and outcome.

Participants regularly referred to the variability of patient circumstances and number of other factors that influenced resource use and outcomes. For example, burns patients may often be either

elderly, paediatric or have issues with mental health, substance abuse or challenging social circumstances. As burns care is a specialist service patients may be referred from a considerable distance, especially to Burn Centres. Such non-clinical factors will have a particular influence on (for example) length of hospital stay and compliance with outpatient care. Comorbidities and non-uniform burn depth are common and mean that the patient populations defined for the modelling are significantly different from real patient populations. Data from more homogeneous populations, as used in well-controlled trials, are obviously more suited to providing data for economic models, which involve inherent simplification of the patient pathway.

3.2.4 Group A patients – 10% TBSA partial thickness burns, not requiring grafting

Our questionnaire was based on information gathered during the assessment report. However it became clear that the assumption that patients with a partial thickness burn of 10% TBSA would be treated in theatre was erroneous. Most adults have such an injury cleaned and treated with conventional dressings on the burns ward by nurses, using oral or inhaled analgesia and possibly sedation. Children are more commonly taken to theatre and treated with Biobrane. Some adults may also have Biobrane but in most services this is rare.

The interviewee responses are summarised in Table 5 for adult patients. Most participants felt that ReCell had no place in the treatment of this type of burn as these should normally heal without complication within 2 weeks. Alternative treatments were thought to have no impact on clinical outcomes. Differences in patient pathways between sites were occasionally conspicuous. For example, in one site adult patients with these injuries were likely to be treated using conventional dressings on the burns ward and sent home the same day, whereas in another site burns greater than 5% TBSA were considered for treatment in theatre, requiring a general anaesthetic (GA), surgical team and a minimum of a couple of days hospital stay.

Table 5: Data summary for 10% TBSA partial thickness burns in adults

	Conventional	ReCell¹	Biosynthetic²	ReCell + Biosynthetic³
Treatment	Most often treated on the burns ward by nurses, with a review by burns surgeon. Three sites indicated a greater likelihood of patients being taken to theatre for treatment. Variety of dressing types used, mostly silver-containing.	Would generally require a GA and treatment in theatre with surgical team. Would require 20-30 mins longer than conventional treatment in theatre and may be associated with greater likelihood of Versajet use. Telfa Clear used as interface dressing, antimicrobials not used or reduced. Additional dressing for the donor site.	Would generally require a GA and treatment in theatre with surgical team. Would require 20-30 mins longer than conventional treatment in theatre and may be associated with greater likelihood of Versajet use. Biobrane may be covered with additional dressing or simple gauze.	Similar to ReCell

¹ Extremely limited use in this patient group. Based on two interviewees; one had been involved with a single patient the other used ReCell most often in children with darker skin types.

² Uncommon for adults in most sites.

³ Based on one interviewee.



	Conventional	ReCell¹	Biosynthetic²	ReCell + Biosynthetic³
Dressing changes	Dressings changed generally every 2-3 days, usually requiring 1-2 nurses. Generally requires oral and/or inhalational analgesia/sedation. Depending on the type of interface dressing and quantity of exudate, only secondary dressings may be changed.	<i>Same as conventional dressings.</i> Try to leave interface dressing undisturbed for 5-6 days. Donor site dressing may stay on until healed.	<i>Same or slightly reduced frequency.</i> Outer dressings changed – Biobrane lifts off as wound heals. Generally faster and less painful than conventional dressings.	<i>Same as Biobrane.</i> Donor site dressing may stay on until healed.
Length of stay	Typically 4-6 days, range of 0-7 days. Adults are often treated as outpatients in 1 site, but in most cases they stay until the 1 st or 2 nd dressing change.	<i>Same as conventional dressings.</i>	<i>Generally same as conventional dressings, maybe slightly reduced.</i>	<i>Same as Biobrane.</i>
Healing	'By definition' in 7-14 days	<i>Same as conventional dressings for burn wound.</i> Donor site takes 7-10 days to heal.	<i>Same as conventional dressings.</i>	<i>Same as conventional dressings.</i>
Need for patch grafting due to poor healing	This would only occur if the initial burn depth assessment was incorrect or the wound became infected. Estimates between 0-10% of patients.	<i>Same as conventional dressings.</i>	<i>Same as conventional dressings.</i>	<i>Same as conventional dressings.</i>
Hypertrophic scarring	In general considered due to incorrect depth assessment – most likely in deeper areas that take longer to heal and/or require a graft. Variable estimates from 0-30%.	<i>Same as conventional dressings.</i>	<i>Same as conventional dressings.</i>	<i>Same as conventional dressings.</i>

Paediatric patients were:

- more likely to have Biobrane as a treatment option
- more likely to have early dressing changes in theatre under general anaesthetic
- may not require as many theatre staff as adults and may take less time for procedures
- likely to have a play specialist present during procedures when they were awake
- may have a shorter length of hospital stay (range 1-5 days) as they are more likely to receive Biobrane and to have carers at home.

Biobrane was used primarily for its pain relieving properties and was not thought to contribute to faster healing, reduced need for later patch grafting procedures or improved scar outcomes by most interviewees. One interviewee indicated that Biobrane was associated with a more supple scar in the long term that was less prone to breakdown. Biobrane may contribute to shorter length of stay due to the ease and reduced pain of dressing changes, although it does require additional resource use initially due to the need for surgical treatment under a general anaesthetic.

Those participants who would use ReCell in this patient group indicated that ReCell required a surgical procedure under general anaesthetic, with additional procedure time compared to conventional dressings applied in theatre. These participants could not substantiate any clinical benefits in terms of reduced healing time, reduced need for later patch grafting or improved scar outcomes. There was no indication of resource saving in terms of reduced dressing changes or nursing time.

3.2.5 Group B Patients – 10% TBSA deep dermal or full thickness burns expected to require meshed grafting

We found that most interviewees were likely to use sheet autografts rather than meshed ones in this size burn. The decision whether to mesh or not depended on burn location (complex areas, contouring or the need for enhanced cosmesis) and the expected amount of bleeding or exudate. Grafts may also be meshed or fenestrated with little or no actual expansion in order to improve adhesion. ReCell would not be used in combination with a sheet graft. Almost all interviewees indicated that ReCell, alone or with Biobrane, was not an appropriate treatment in this patient group (i.e. as an alternative to autografting) as it did not provide any replacement dermis. ReCell use was therefore uncommon in this group of patients. The interviewee responses are summarised in Table 6 for adult patients.

Table 6: Data summary for 10% TBSA deep partial thickness or full thickness burns in adults

	Autograft	Meshed graft + ReCell
Treatment	Generally a sheet autograft; may be meshed 1:1.5 or 1:2 occasionally. Takes 1-2.5 hrs in theatre with 2 surgeons and a surgical team. Variety of dressing types used for burn and donor site wounds.	ReCell adds at least 15-30 mins to the operating procedure time. Low adhesion dressings generally used.
Dressing changes	First wound check is generally at 2-5 days. In some sites 5-20% of patients may have this done under GA with a surgical team. Otherwise IV, oral and/or inhalational analgesia/sedation is used. Later dressing changes are every 2-3 days. Depending on the dressing type and the amount of exudate only outer dressings may be changed. Ward or outpatient dressing changes are conducted by 1-2 nurses.	<i>Same as for autograft.</i>
Length of stay	Most patients can go home by the second dressing change. Typically 5-7 days, range of 4-14 days.	<i>Same as for autograft.</i>
Healing	Around 10-14 days for the burn wound, but small patches may still require dressings for up to 21 days. 10-14 days for the donor site.	<i>Same as for autograft.</i>
Need for grafting due to poor healing	5-15% of patients. This is generally related to infection.	<i>Same as for autograft.</i>
Hypertrophic scarring	Around 15-50% of patients. Some sites indicated that all grafted patients get scar management (pressure garments, silicone creams).	<i>Same as for autograft.</i>

Paediatric patients were:

- more likely to have sheet autografts
- likely to require slightly less time in theatre
- more likely to have early dressing changes in theatre under general anaesthetic
- likely to have a play specialist present during procedures when they were awake
- more prone to hypertrophic scarring.

The addition of ReCell to meshed autografts in this patient group was not associated with any clinical benefits or resource saving.

3.2.6 Group C Patients – 40% TBSA deep dermal or full thickness burns expected to require wide mesh grafting

Excision and coverage of the entire burn area within 3 days is the prime intent of initial treatment in these patients. If insufficient suitable donor sites are available initially, temporary wound cover is used until the patient is taken back to theatre (e.g. different patient position or additional consent taken) or donor sites are healed sufficiently to allow re-cropping. If a skin biopsy is taken for laboratory culture then cultured cells are generally available from around 14 days onwards, but this does not delay treatment. Therefore in a site that routinely cultures cells for all such burns, the first areas treated will not receive cultured cells. Cultured cells are only available from one NHS laboratory and one commercial provider. The interviewee responses are summarised in Table 7 for adult patients.

Table 7: Data summary for 40% TBSA deep partial thickness or full thickness burns in adults

	Meshed autograft	Meshed autograft + ReCell	Meshed graft + Cultured Cell
Treatment	Around 1-3 operations in the first week. Generally requires 2 surgical teams including 3-4 surgeons. Autograft mesh ratios are generally 1:1.5 to 1:4. These are dressed with allograft or a variety of commercial dressings. Allograft, Biobrane, skin substitute or other dressings are used for temporary cover.	<i>Same operations as meshed autograft.</i> Telfa may be used as interface dressing. No silver dressings directly on cells.	Cultured cells used for minimum of 25-40% TBSA in most sites. <i>Same operations as meshed autograft.</i> Telfa may be used as interface dressing. No silver dressings directly on cells.
Dressing changes	Initial dressing changes are conducted alongside and in between treatment operations. Dressing changes are conducted in theatre under GA for between 1-4 weeks.	<i>Same as for meshed autograft.</i>	<i>Same as for meshed autograft.</i>
Length of stay	Around 3-6 weeks in total ⁴ . Patients are at least 95% healed before discharge. Around 1 day/% TBSA for younger fitter patients.	<i>Same as for meshed autograft.</i>	<i>Same as for meshed autograft.</i>
Healing	See length of stay. Depends on number of operations and delays between them. Patients may need up to another month of outpatient wound care.	See text	See text
Need for patch grafting due to poor healing	33-100% of patients.	<i>Same as for meshed autograft.</i> ReCell may be used instead of autograft for smaller areas.	<i>Same as for meshed autograft.</i> Cultured cells may be used instead of autograft for smaller areas.
Hypertrophic scarring	Generally all patients have some hypertrophic areas, maybe 15-33% need corrective surgery.	See text	See text

The clinical pathway for this patient group was more variable and difficult to describe. Data from iBID indicates 716 patients with 40% or greater TBSA injury from 2003 to 2013; an average of around 8 or 9 patients per year per Burn Centre. Therefore providing estimates in this group was especially difficult for interviewees. Burn injuries of this extent are commonly associated with inhalational and other injuries; length of hospital stay is particularly affected by such factors. The use of skin

⁴ If solely dependent on skin burns.

substitutes is more common and the difference between adult and paediatric patients is less marked in this patient group.

The rationale for the use of both cultured cells and ReCell on top of meshed autografts is to increase the speed of healing and improve the appearance in the interstices. Interviewees voiced an *expectation* of faster healing, but were unable to substantiate this with estimates of healing time. There was the suggestion that early healing (at round 2 days) and/or early scar appearance may be slightly improved, however interviewees generally indicated that they did not notice any long term difference in appearance between meshed autografts with and without cells. Three interviewees noted that *if* healing time were reduced then there was potential for improved scar outcomes.

In general ReCell was considered for use where larger mesh ratios were required and cultured cells were not available. Several interviewees indicated that cultured cells were preferable to ReCell, citing the increased volume, concentration and viability of cultured cells. Three interviewees described ReCell as ideally only for use on pieces of donor skin that were not needed for autografting and would otherwise be discarded. The use of ReCell on donor sites was contentious; some interviewees cited published and local evidence that ReCell can reduce donor site healing time by about 24 hrs. However it was debateable whether this difference would be clinically significant.

3.3 Summary of effect of ReCell on specific parameters

We summarise here the evidence from the assessment report, additional literature search and the expert survey for the claimed or potential benefits and detriments of the use of ReCell in acute burns and scalds.

3.3.1 Theatre time and resources

Gravante et al. (2007) and Rawlins (2013) both indicated an increase of around 30 minutes in the operating procedure time using ReCell alone as an alternative to autografts. The interviewees here also consistently supported the need for extra time in theatre when ReCell was used as an adjunct to meshed autografts. Two interviewees indicated that either an additional staff member was required or the organisation of the staff and space in theatre would need to be altered to allow for the processing of the biopsies. A 10% TBSA burn in an adult would equate to approximately 1800 cm² (Sacco et al. 2010), requiring 6 ReCell kits for full coverage. We conclude that the use of ReCell incurs additional resource use in terms of theatre time, staff time and consumables

3.3.2 Graft donor size and depth

No information about graft thickness was collected. Gravante et al. (2007) demonstrated that, when used as an alternative to autografting, ReCell results in a smaller and less painful donor site. This follows logically from the method of use and is uncontentious. However, if ReCell were used in Group A patients this would require an additional (if small) donor site, as the other treatments do not require donor skin. When used as an adjunct to meshed autograft there is no reduction in the size of the donor site. Interviewees indicated that samples for use in ReCell kits would not increase the size of the donor site taken but would use otherwise unused pieces of donor site skin. Interviewees stated that the availability of ReCell did not influence the mesh ratio chosen for the autograft, i.e. surgeons would not use a higher mesh ratio plus ReCell *in order to* create a smaller

donor site. We conclude that the use of ReCell would only reduce donor site size if it were used as an alternative to autografts, and this indication is not supported by interviewees.

3.3.3 Pain and analgesia

Wood et al. (2012) reported improved pain scores (not statistically tested) with Biobrane alone or Biobrane plus ReCell versus conventional dressings in children with partial thickness scalds not anticipated to heal within 10 days. Patients with deep partial thickness burns treated with ReCell or ReCell plus Biobrane have reduced pain or analgesia requirement in comparison to autografts (Gravante et al. 2007; Rawlins et al. 2011). However the former does not demonstrate any additional benefit for ReCell over Biobrane and the latter is attributable to the reduced donor site size with respect to autografts. Interviewees here reported no effect of the use of ReCell on pain or analgesia requirements or the requirement for patients to have a general anaesthetic during dressing changes. We conclude that when ReCell is used as an adjunct to meshed autografts in deeper burns or as an alternative to conventional dressings in partial thickness burns there is no clinical or resource benefit related to pain. When ReCell is used in conjunction with Biobrane there is no pain-related benefit beyond that from using Biobrane alone.

3.3.4 Dressing changes

In the scope the sponsor claimed that the use of ReCell reduced the frequency of dressing changes from daily to weekly. Wood et al. (2012) reported a reduction in the number of dressing changes (not statistically tested) for both Biobrane and ReCell plus Biobrane with respect to conventional dressings in children with partial thickness scalds not anticipated to heal within 10 days. The sponsor's economic model separated dressing changes into £166 for a conventional dressing change and £25 for dressing changes for the other treatments (ReCell alone, Biobrane alone and Biobrane plus ReCell); the basis for these costs was unclear (see assessment report, p55).

Interviewees were specifically asked about the frequency, duration, staff resources and nature of the dressing changes to determine any effect of ReCell on these parameters. Interviewees here did not report a reduction in the frequency of dressing changes or a reduction in healing time (and therefore number of dressing required) with the use of ReCell in any patient group, nor any difference in resource use. Most sites would inspect the burn wound at around 2 days post-intervention, which would require at least secondary dressing changes. Some interface dressings are clear and allow wound inspection without removal. Some interviewees indicated that they would avoid disturbing autografts or cells for up to 5 days but that outer dressings would be changed in the meantime. In Group C patients early dressing changes tended to be interspersed between, or conducted during, operations to provide burn wound treatment. Differences between sites, between different interface dressings and between patients (with different injury sites, levels of exudation and pain tolerance) introduce substantial variability in the resource implications for dressing changes. We conclude that there is no demonstrable benefit of the use of ReCell on the frequency, type, number or other resource use for dressing changes.

3.3.5 Healing of the donor site

We found no evidence to suggest that the ReCell donor site would heal faster than an autograft donor site, although we accept that as an alternative to autografts ReCell requires a substantially smaller donor site that may heal faster. Interviewees here referred to a potential reduction in time

to healing of autograft donor sites that were treated with ReCell or cultured cells. One interviewee referred to a controlled trial reporting a 24 hr reduction in healing time with the use of ReCell. The EAC was unable to locate a paper that fitted this description. The Avita website refers to a study in which surface electrical capacitance measurements are used to quantify the healing rate of donor sites treated with cultured cells versus cell medium (Magnusson et al. 2007). However, this study does not report time to healing or use ReCell. Another interviewee stated that although a local audit of cell use had not shown any clinical benefit of their application, anecdotal evidence showed that donor sites in children could be re-cropped at one week when cells were used. Other interviewees also indicated an expectation of faster healing of donor sites with the application of ReCell or cultured cells, but could not substantiate this with evidence from their own practice. We conclude that there is potential for faster healing of donor site wounds that are sprayed with ReCell, although evidence is poor and the clinical significance of this is debatable.

3.3.6 Healing of the recipient burn wound

Wood et al. (2012) reported reduced time to healing and increased rates of healing at 10 and 21 days (not statistically tested) with Biobrane alone or Biobrane plus ReCell versus conventional dressings in children with partial thickness scalds not anticipated to heal within 10 days. Rawlins et al. (2011) reported a reduced time to healing (not statistically tested) in 4 patients with deep dermal burns treated with Biobrane plus ReCell compared to 10 patients treated with meshed autograft. However, given the criticisms of this evidence detailed in the assessment report, there is no evidence that ReCell improves speed of healing over and above any benefit that may be conferred by the use of Biobrane. Gravante et al. (2007) reported no difference in time to healing between deep partial thickness burns treated with ReCell alone and with autografts. The sponsor's economic model used the data from Wood et al. (2012) to estimate a percentage reduction in healing time for ReCell alone, Biobrane plus ReCell and Biobrane alone versus conventional dressings.

The interviewees here indicated no difference in burn wound healing time in any of the patient groups. Advocates of both cultured cells and ReCell indicated that the rationale for the use of cells as an adjunct to meshed autografts was to achieve faster healing and improved aesthetic appearance. However, when pressed for estimates these interviewees were not able to substantiate this approach with numbers from their personal experience. Phrases such as 'anecdotally', 'we expect that', 'we hope that' and 'the science is reasonable that' were used. One ReCell user noted that quicker healing might be apparent at around 2 days but that the range of healing times was not different. Another interviewee provided the sole quantifiable estimate of benefit of the use of cells in the Group C population:

"That's hard to say isn't it? Say it would speed it up by one and a half times. It makes a significant difference to have them than not have them. I use the cultured cells more, but I think having the ReCell in these situations is very good as well."

However, this interviewee indicated that the range of other factors that influenced hospital stay meant that faster healing would not necessarily translate into shorter hospital stay.

There was contention about the mechanism of effect of cell application – whether it was the cells that proliferated and covered the wound or whether it was (e.g.) growth factors that the cells produced. One interviewee was aware of a recently completed randomised controlled trial of

cultured cells in burns. The EAC contacted the investigator in this study and requested additional information on the basis that the rationale for any potential benefit of ReCell on speed of healing and long term scar outcomes (with the exception of pigmentation) is similar to that for cultured cells. Publically available information indicates that this is an intra-patient 4-way randomised comparison of 1:4 meshed autograft alone versus meshed autograft plus sprayed cells, cell sheets and sprayed solution (Maitz et al. 2014).



The EAC did not conduct a literature review of the use of cultured cells in burns treatment.

Despite a general expectation of benefit in terms of speed of healing amongst users of cultured cells and ReCell in larger burns we conclude that there is no evidence from expert opinion that this has been realised in actual practice.

3.3.7 Length of hospital stay

In the sponsor's economic model 50% of patients treated with conventional dressings remained as inpatients until healed versus 25% of patients who received the alternative treatments (ReCell alone, Biobrane alone or ReCell Plus Biobrane). This was based on the assumption that these treatments require only secondary dressing changes and was challenged by both the EAC and the lead team expert advisers. Park et al. (2013) reported a reduced length of stay for patients treated with ReCell alone versus patients treated with autograft, although the authors state that different indications and timings for these treatments mean that this outcome should "be interpreted cautiously".

Interviewees here indicated that the type of treatment would have no effect on the length of hospital stay or the need for intensive/high dependency care. They were keen to point out that the patients described in the questionnaire were not typical and that there were many reasons for keeping patients as inpatients other than the condition of their skin burns; e.g. difficult social circumstances, mental health issues, co-morbidities, substance abuse, inhalational and other injuries, long journey times, complex wound management (not delegated to community nursing), need for physiotherapy. These factors are most likely to confound length of stay in the largest burn population. We conclude that there is no evidence of benefit of the use of ReCell on length of stay or need to remain as an inpatient.

3.3.8 Need for patch skin grafting

Wood et al. (2012) reported lower rates of autografting at 10 days (not statistically tested) for both Biobrane and Biobrane plus ReCell versus conventional dressings in children with partial thickness scalds not anticipated to heal within 10 days. This patient group is difficult to compare to the patients populations considered in this work. Group A patients are those expected to heal within 2 weeks and not expected to need grafting. Group B and C patients are expected to need grafting and would be treated within 1-2 days. It may be that the patients in Wood et al. (2012) are closest to intermediate, indeterminate or mid-dermal burns in which the need for grafting is not initially clear. This patient population is not considered in this project.

The sponsor's economic model used published data for the conventional dressings and estimates from their own expert advisers for the other treatment types to populate the proportion of patients progressing to skin grafts in their economic model. The base case estimates were 30% for conventional dressings and Biobrane alone and 10% for ReCell alone and ReCell plus Biobrane. The interviewees here provided estimates that were much lower, but quite variable and they also noted its dependence on factors such as infection and the accuracy of the initial burn depth assessment. However, none of the interviewees indicated an effect of the treatment type on the requirement for later patch grafting. We conclude that this parameter is particularly difficult to estimate and highly dependent on the nature of the injury. There appears to be no evidence to suggest that the use of ReCell affects the effectiveness of burn wound healing or graft take and therefore the need for additional surgical treatment at around 10-14 days.

3.3.9 Long term scar outcomes, including pigmentation

In the assessment report all published data that reported long term scar outcomes indicated comparable results between different treatment options. Gravante et al. (2007) reported no difference in simplified Vancouver Scar Scale (VSS) and number of contractures between ReCell alone and autografts at 6 months. Wood et al. (2012) reported individual VSS values for 4 patients in each of three treatment arms at 6 months (ReCell alone, ReCell plus Biobrane and conventional dressings) that do not appear to differ. Rawlins et al. (2011) reported VSS values at 6 months of 5.3 for ReCell alone and 6.5 for autografts (not statistically tested). VSS values range from 0 (normal skin) to 13 (worst scar possible) and as the variance of their data is unknown the EAC does not consider this difference to be significant. Sood et al. (2011) reported modified VSS at 12 months in 10 patients in an intra-patient comparison of ReCell alone versus autograft. Pigmentation, colour match and modified VSS were comparable for the two treatments, with 1 out of 10 patients indicating a preference for the appearance of the ReCell-treated site.

Interviewees here indicated no effect of treatment type on the incidence of hypertrophic scarring. Incidence increases with time to healing; in a retrospective audit Cubison et al. (2006) reported an incidence of 0% in children with scalds that took less than 10 days to heal (n=55), whereas it was 8% for 10-14 days (n=79) and 20% for 15-21 days (n=75). Interviewees indicated that in Group A injuries incidence should be very low and would be related to wound infection and inaccurate assessment of the wound depth. In deeper burns that are grafted, incidence is higher and in large and full thickness burns interviewees indicated that some areas of hypertrophic scarring are to be expected.

Some interviewees were of the opinion that the use of any cells did not affect long term appearance, quality or function of burn scars. There was also the view that *if* time to healing was reduced by the addition of cells then improved scar outcomes could be expected. One interviewee described more flexible and softer scars when cultured cells were used with skin substitute and an expectation of a similar effect with ReCell, but could not attribute this outcome directly to the use of cells.

Pigmentation outcomes were also equivocal for ReCell use in acute burns. Many interviewees did not think that ReCell made any difference to long term pigmentation. One indicated that they had not considered this outcome specifically in relation to ReCell use. Two noted that pigmentation may recover slowly over 2-3 years. Three indicated that they might be more inclined to use ReCell in patients with darker skins. The most positive expert opinion was:

“We’ve had some encouraging results, but we’ve also had occasional results where it’s not been obvious that it helps. So I can’t say definitively that it always improves repigmentation. But that partly, I feel, again depends a bit on the depth of the burn and how much normal reservoirs of melanocytes are left...Yes, anecdotally we do feel that it can improve pigmentation post burn.”

We conclude that there is no evidence to support the claim that the application of ReCell results in systematically improved long term scar outcomes, including pigmentation. There is the suggestion that shorter term scar outcomes may be slightly improved.

3.4 Applicability of outcomes from repigmentation indications

The sponsor’s submission included published evidence for the use of ReCell in hypopigmented lesions (vitiligo and chronic scars) that the EAC determined to be outside the scope of the evaluation. However, the specification for this project requested additional expert opinion as to whether this evidence should be considered relevant. Pigmentation outcomes were felt to be of particular importance to patients with darker skin and this was noted in the special considerations in the scope. The EAC has reviewed three comparative studies of the use of ReCell in vitiligo (Section 3.1.2) and concluded that the repigmentation outcomes are equivocal.

In general interviewees here indicated that there was a substantial physiological difference between an acute burn and a surgically created wound in (e.g.) vitiligo or hypopigmented scars. A burn wound was a less ideal environment, with potential contamination and variable depth. However, opinion was divided about whether outcomes were transferable between indications. Several interviewees stated that they did not think that ReCell had any positive effect in vitiligo, whereas others stated that they had seen some positive effect in their own vitiligo patients. *If* ReCell could be shown to have a benefit in hypopigmented conditions then even some sceptical interviewees stated that they might consider it for this reason in acute burns.

3.5 Role of ReCell in burns care in the UK

Interviewees were additionally asked about what role they felt ReCell had in the treatment of acute burns and where any potential benefit might lie. All interviewees were open to the possibility that ReCell may have some benefit. The options for this were:

- Large burns that require grafting – 7 interviewees either had used it in this way or would consider it. ReCell is readily accessible in the early stages of wound cover when cultured cells are not yet ready or in burn services that did not have easy access to such laboratory services. Also, ReCell can be used for ‘left over’ pieces of donor skin that are not suitable for grafting and would otherwise be discarded. However this use has the disadvantage of occurring towards the end of a surgical procedure and therefore extending theatre time.
- Mid-dermal, mixed depth, intermediate or indeterminate burns – 2 interviewees had used it in these injuries in the hope of speeding up healing in comparison to conservative treatment and reducing the need for later autografting.
- Deep facial burns – 1 site had used it in this indication. A very conservative, non-grafting approach was generally used in these cases and ReCell was described as a ‘last ditch’ treatment where the burn had not healed well after about 2 weeks. Echlin et al. (2012)

reported a case series of 4 patients with facial burns who were treated with ReCell at 9-11 days post injury and indicated positive outcomes (see assessment report, p32).

Several interviewees had used, or were considering using, ReCell for treating hypopigmented scars or vitiligo.

3.6 Economic modelling

The primary purpose of this project was to obtain data with which to populate an economic model for the use of ReCell in acute burns. The EAC was unable to do this as virtually no quantitative data for clinical benefit or resource saving was obtained from the survey of clinical experts. Essentially interviewees were either of the opinion that ReCell did not provide any additional clinical benefit or resource saving over the comparator treatments, or were unable (or unwilling) to provide numerical estimates.

The use of ReCell would incur a cost of £950 per kit (each treating up to 320cm²) and require additional time in theatre, whether it was used as an adjunct to meshed grafting in deeper burns or as an alternative to conventional dressing in shallower burns. The EAC has been unable to identify any evidence to support clinical benefit or resource savings resulting from ReCell use (with respect to the comparator treatments) that would balance or outweigh these additional costs in the three patient populations defined here. We have further determined that the economic model in the sponsor's submission was inappropriate as it included a patient population in which almost all expert advisers indicated they would not use ReCell.

4 Discussion

4.1 Summary of findings regarding use of ReCell in acute burns

No new data about the use of ReCell in acute burns was obtained from published literature or existing UK databases. Expert opinion was collated from 10 UK NHS burns specialist clinicians by using a questionnaire and semi-structured interviews. In general these experts did not express any quantifiable benefits from the use of ReCell in comparison to current standard practices. ReCell was not in common use amongst participants, but even those with the most experience and positive opinion of the technology could not substantiate their expectation of improved clinical outcomes with estimates from their own practice.

4.2 Comparison with findings from assessment report/November MTAC meeting

In the assessment report the EAC concluded that in partial thickness burns ReCell alone or in combination with Biobrane was not shown to be clinically superior to Biobrane alone. The cost savings of ReCell alone or ReCell plus Biobrane versus conventional dressings that were identified in the sponsor's economic model in partial thickness burns were based on estimates and assumptions that are seen to be erroneous in the light of information from a wider base of expert advisers.

In the assessment report the EAC also concluded from the published evidence that ReCell was at least as clinically effective as the use of split thickness autografts in mid to deep dermal burns, and

was a suitable alternative treatment. In this context the use of ReCell was associated with a smaller donor site wound and related pain. The UK expert advisers consulted here were consistent in their opinion that it was not appropriate to use ReCell directly on deep partial burns and that it should only be used in these injuries on top of meshed autograft. The disparity between the published evidence (mostly non-UK) and this opinion has not been explained. It may be due to differences or ambiguities in the description of the burn injury or in national approaches to burn care. The EAC has attempted to contact the authors of the studies to clarify this but has not received any responses. The outcomes from the use of ReCell as an adjunct to meshed autografts in deeper burns were not addressed in either the published literature or the sponsor's economic model.

The responses of the expert advisers here also contrast with those obtained both by the sponsor and the EAC in the assessment report. The sponsor obtained written estimates of model parameters from 4 clinical experts, one of which was the inventor of the technology. The questions were answered variably, but in general suggested a slight reduction in the proportion of patients with partial thickness burns requiring later autografts. The apparent difference between the information provided to the sponsor and that obtained by the EAC could be explained by:

- Different participants – the sponsor identified clinical users of ReCell (in the UK and Australia) whereas the EAC attempted to obtain information from each relevant burn service in the UK. There were also 4 expert advisers identified by NICE for the assessment report. Of these 2 were also in the sponsor's group, but only one of these contributed to the EAC's survey. The other adviser provided written evidence for the assessment report in which they considered that ReCell was clinically beneficial and also agreed to participate in the expert survey here, but did not respond in the available time.
- Different methods – the sponsor collected data from their expert advisers by providing a written set of questions. Some advisers responded briefly and others provided longer explanations and qualifications to their answers. Occasionally they responded to the same question in different terms (see assessment report, Table 12). The EAC conducted semi-structured interviews which allowed the interviewer and participant to explore the underlying information and to adapt when the assumptions or questions were found to be inappropriate. Respondents may have found it more uncomfortable to provide unsubstantiated numerical estimates in discussion (and 'on the record') than when filling in a table. There is also more scope for misunderstanding by the respondent and the investigator when only written communication is used. This was apparent when one of the survey interviewees completed the first part of the questionnaire by hand and was then interviewed for the rest of the questionnaire.

4.3 Strengths and weaknesses of the study design

The initial study design for this work was appropriate to answer the specification given the short timescale available. The method was altered as the work progressed in response to the non-availability of the burn injury database and the nature of the data being collected.

The survey of clinical expert advisers could have been improved methodologically by piloting the questionnaire or by conducting it as a two-part survey. The short timescale for the project and the difficulty of obtaining rapid responses from busy clinicians precluded both of these approaches. As a

result the questionnaire was not ideally suited for completion by hand and was also found to be based on assumptions that were not always appropriate to local care pathways. The EAC considers that if a more robust survey had been conducted it is unlikely that it would have identified additional useful data as it was primarily respondents' opinion of the technology and their ability to estimate values that precluded the attainment of suitable data.

We did not achieve 100% coverage of UK Burn Centres and Units. Five additional clinicians initially agreed to participate but did not respond to the questionnaire or the invitations for telephone interview. The short timescale and lengthy nature of the questionnaire are the most likely reasons for non-participation. We also did not include burns services in Scotland or Northern Ireland. An alternative strategy for identification of expert advisers would have been to ask the manufacturer or distributor for a list of UK users of ReCell and compared these to other services. We chose to attempt to enlist all specialist Burn Centres and Units in England and Wales and allow the consultant surgeons at each to determine who would participate. In doing so we assumed that each respondent would have a reasonable knowledge of the practice and outcomes of colleagues at their site.

Despite applying as early as possible we did not obtain access to NBID/iBID due to the short timescale. Initially, publically-available information suggested that appropriate resource-use data was included in this database (Evolution Healthcare Systems), but later discussion with the database owners indicated that these fields may not be well-populated yet. Also it is unlikely that information regarding treatment with ReCell would be recorded there. We did obtain some general reports from the owners, but this aggregated information is of little use for economic modelling. It is probable that existing local and national datasets may be obtained if more resources were available. However, one interviewee did refer to a local audit that indicated no clinical benefits for the use of cells.

We did not conduct the intended targeted literature search. As we became aware that the expert survey was not providing the required quantitative data we decided not to continue with this part of the project. As no new ReCell data since the assessment report had been identified this search would only have provided additional data for the comparator treatments.

The patient populations defined in the specification did not appear to be entirely appropriate for the evaluation of ReCell. In the UK it appears that most burn surgeons who use ReCell reserve it for larger burns. The EAC definition of the Group C population as 40% TBSA may have been rather low, although practice varied between services in terms of the threshold for cultured cells use or the mesh ratios used. However, with increasing burn area the number of patients becomes smaller and the variability in the injuries increases. Fewer burn services are involved in the care of these patients (Centres only) and data collection becomes more difficult. Also interviewees here provided no indication that they could substantiate any potential benefit of the use of cultured cells or ReCell in these or in larger burns. The EAC defined the Group B population as 10% TBSA based on prior information that autografts for this size burn are likely to be meshed. However, most interviewees indicated a preference for sheet grafting at this burn size.

Several interviewees were vocal in their antipathy for the use of ReCell in the treatment of acute burns, although many also stated that they would like to see well-conducted trial evidence. In the absence of such data, it is unlikely that burns services would be convinced to change their current practice. Proponents of ReCell were open about the lack of data to back up their hopes and

expectations of clinical benefit. There is some wide variation in clinical practice and the complexity of factors that influence outcomes and resource use in patients requiring specialist burn services means that any potential benefits or detriments may not be realisable in actual use.

The EAC concludes that the information provided by the expert survey indicates no perceived benefit for ReCell for an increase in resource use.

4.4 Research ideas

Many of the interviewees noted the difficulty of conducting research in patients with burn injuries. Wood et al. (2012) attempted to conduct a three armed randomised controlled trial including ReCell but failed to recruit sufficient patients for an effective study. Problems with research in this patient population include variability in burn type, size, location and depth, possible contamination with accelerants, complex social circumstances and issues with mental health conditions. Other difficulties are shared with general wound healing research such as the high number of available treatment options (e.g. dressings and topical treatments) and ambiguous outcome measures (e.g. healing).

The question of which patient population would be most appropriate is also non-trivial. Smaller partial thickness burns are more common and therefore would be easier to recruit in suitable patient numbers. Alternatively variability of the wound could be accounted for by conducting a study in donor site wounds. However clinicians are unlikely to want to use an expensive technology to treat an injury that should heal without complication. Also even if such a study were to demonstrate clinical benefits for ReCell it may be dismissed by clinicians as not relevant to actual clinical practice. In larger burns low and unpredictable patient numbers suggest the need for multi-centre studies or long study durations, and large travelling distances to these specialised services could frustrate the long term follow up that would be required to determine the effect of ReCell on pigmentation and other scar outcomes. The mid-dermal or intermediate/indeterminate depth burns may be most suited for the determination of potential clinical benefit from the use of ReCell, but this type of injury and its treatment are likely to be particularly variable. Large numbers of patients may be required to overcome this.

There is potential for the use of iBID/NBID or local data resources in future research. The availability and suitability of such sources is not known, but they may not contain sufficiently specific information to inform further evaluations of ReCell.

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5 Appendix 1 - expert adviser questionnaire

To understand what the variability in practice is we have asked for an average and a range – the range should reflect typical patients, not the extreme values (e.g. typical length of stay might be 5 days with a range of 2-10 days for most patients). We are especially interested in differences between the options (e.g. if theatre time for biosynthetic dressing is 1 hour but it takes another ten minutes if ReCell is also being used).

1. Pigmentation outcomes:
 - a. Does ReCell affect long term pigmentation of the healed burn wound compared to standard treatment? If so, how?
 - b. Does the skin colour of the patient affect your decision to use ReCell? If so, how?
 - c. ReCell has also been used to try to treat hypopigmentation in established scars and in stable vitiligo (repigmentation). Do you believe that outcomes from the use of ReCell in such repigmentation treatments can be used as surrogates for outcomes in burns? I.e. if the use of ReCell improved pigmentation in non-burn indications would you realistically expect to see the same improved outcomes if it were used in acute burns?

Group A patients: 10% TBSA partial thickness burns that are not expected to require grafting

The burn does not involve complex areas (e.g. face, hands, genitals) and has no obvious infection. Patients' length of stay and care is dependent only on their skin burn wounds, i.e. there are no other injuries (e.g. inhalational, fractures), difficult social circumstances or large distance to home that preclude discharge.

Assumptions:

- Patients go to theatre within 2 days (48 hours) post injury.
- All surgical treatments require the same wound preparation.
- Patients stay as inpatients until the first dressing change post-procedure.
- Inpatients remain on the burns ward until discharge.
- Any patient that requires their first dressing change to be carried out in theatre under a general anaesthetic (GA) will remain as an inpatient and that those who only require simple analgesia will be discharged to outpatient care.
- Any patient requiring later surgical intervention for unhealed burns will only require one instance of treatment to achieve healing.

Treatment options:



The burn can be treated in one of four ways:

- conventional dressings,
- ReCell plus conventional dressings (e.g. Telfa),
- biosynthetic dressing (e.g. Biobrane) alone,
- ReCell plus biosynthetic dressing.

2. Are any of the assumptions nonsensical?

3. Are any of these treatment options nonsensical?

Group A: 10% TBSA partial thickness		Conventional Dressing		Difference from conventional dressing					
				ReCell + conv. dressing		Biosynthetic dressing		ReCell + biosynth. dressing	
		Avg	Range	Avg	Range	Avg	Range	Avg	Range
Initial surgical treatment	4. How long would you expect the surgery to take (procedure time)?								
	5. How many & what staff would you expect to need in theatre? (E.g. consultant surgeon, trainee surgeon, anaesthetic staff, ODA/ODP, scrub nurse, other.)								
	6. How is the burn wound dressed? a. Primary (contact) dressing b. Secondary (protective) dressing								
	7. How is the ReCell donor site dressed?	NA		NA		NA		NA	
	8. What are the differences in consumables used between treatment options (excluding the ReCell kits)? E.g. maybe contact dressings are stapled, but not Biobrane.								
Dressing changes	9. How many days are there between surgery and the first dressing change/wound assessment?	Avg	Range	Avg	Range	Avg	Range	Avg	Range



Group A: 10% TBSA partial thickness	Conventional Dressing		Difference from conventional dressing					
			ReCell + conv. dressing		Biosynthetic dressing		ReCell + biosynth. dressing	
10. How frequent are dressing changes for the burn wound?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
11. What proportion of patients have their first few dressing changes in theatre under GA?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
a. For how long are these patients likely to require a GA for dressing changes (days)?								
b. What staff are required in theatre?								
c. How long does this take in theatre?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
12. For patients who only require simple analgesia for dressing change on the burns ward:								
a. What analgesia is used?								
b. What staff are required?								
c. How long will this take?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
13. What dressings are changed for the burn wound?								
14. How frequent are dressing changes for the donor site?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
15. What dressings are changed for the donor site?	NA				NA			
Discharge/ Length of 16. What proportion of patients are discharged to outpatient treatment following the first dressing change?	Avg	Range	Avg	Range	Avg	Range	Avg	Range



Group A: 10% TBSA partial thickness		Conventional Dressing		Difference from conventional dressing					
				ReCell + conv. dressing		Biosynthetic dressing		ReCell + biosynth. dressing	
stay		Avg	Range	Avg	Range	Avg	Range	Avg	Range
	17. What is the total length of stay in hospital for this patient population (days)?								
	18. Are there any substantial differences between dressing changes on the ward and those in outpatients (e.g. time required, number/type of staff, analgesia, frequency or dressing type)? Please comment.								
Healing and retreatment	19. For patients with uncomplicated wound healing how long do you expect the burn wound to take to heal (from initial surgical treatment to >95% healing, no further dressings required)?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	20. For patients with uncomplicated wound healing how long do you expect the donor site to take to heal?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	21. What proportion of patients would require secondary surgical intervention (e.g. regrafting) due to poor healing? a. At what point is the decision taken to provide surgical intervention (days post-surgery)?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	b. What are the options for secondary surgical intervention?								
	c. Is the choice of secondary intervention affected by the initial treatment?								



Group A: 10% TBSA partial thickness	Conventional Dressing		Difference from conventional dressing						
			ReCell + conv. dressing		Biosynthetic dressing		ReCell + biosynth. dressing		
d. How does the second procedure differ from the first (e.g. procedure time, size of graft, materials used, staff)?									
e. How long would you expect the wound to take to heal following secondary surgical treatment?	Avg	Range	Avg	Range	Avg	Range	Avg	Range	
22. What proportion of patients do you expect to develop hypertrophic scars?	Avg	Range	Avg	Range	Avg	Range	Avg	Range	

Use of ReCell	23. Are there specific circumstances under which you would or would not use ReCell, other than standard contraindications (e.g. not on burns smaller than 3% TBSA, not on face burns)?	
	24. Does the use of ReCell affect analgesia requirements for background pain?	
Long term outcomes	25. Does the use of ReCell improve the appearance and/or function of the eventual scar? If so, how: <ul style="list-style-type: none"> a. pigmentation outcomes? b. incidence of poor scarring? c. use of conservative scar treatments (creams, compression, steroid injections)? d. requirement for surgical scar revisions? 	



	26. Does the use of ReCell affect any other long term outcomes? (E.g. psychological, need for occupational therapy, need for social services support.) If so, how?	
Source	27. Are your answers in general based on personal recall of experience, access to collected data (e.g. local audit or national databases) or other?	

Additional comments (e.g. on the treatment of this type of patient, on the questions asked or on the use of ReCell)

Group B patients: 10% TBSA deep dermal/partial thickness or full thickness burns that are expected to require (meshed) split thickness skin grafts (SSG)

The burn does not involve complex areas (e.g. face, hands, genitals) and has no obvious infection. Patients’ length of stay and care is dependent only on their skin burn wounds, i.e. there are no other injuries (e.g. inhalational, fractures), difficult social circumstances or large distance to home that preclude discharge.

Assumptions:

- Patients go to theatre within 2 days (48 hours) post injury.
- All surgical treatments require the same wound preparation.
- Patients stay as inpatients until the first dressing change post-surgery.
- Inpatients remain on the burns ward until discharge.
- Any patient that requires their first dressing change in theatre under a general anaesthetic (GA) will remain as an inpatient and that those who only require simple analgesia will be discharged to outpatient care.
- Any patient requiring later surgical intervention for unhealed burns will only require one instance of treatment to achieve healing.

Treatment options:



The burn can be treated in one of four ways:

- meshed split skin autograft (SSG),
- meshed split skin autograft (SSG) plus ReCell,
- ReCell with conventional dressing (e.g. Telfa)
- ReCell with biosynthetic dressing (e.g. Biobrane).

28. Are any of these treatment options nonsensical?

29. Are any of the assumptions nonsensical?

Group B: 10% TBSA deep partial thickness or full thickness		Meshed SSG		Difference from meshed SSG					
				Meshed SSG + ReCell		ReCell alone		ReCell + biosynth. dressing	
Initial surgical treatment	30. How long would you expect the surgery to take (procedure time)?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	31. How many & what staff would you expect to need in theatre? (E.g. consultant surgeon, trainee surgeon, anaesthetic staff, ODA/ODP, scrub nurse, other.)								
	32. How is the burn wound dressed? a. Primary (contact) dressing b. Secondary (protective) dressing								
	33. What mesh ratio is used?								
	34. How large is the donor site (cm ²)?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	35. How is the donor site dressed?								



Group B: 10% TBSA deep partial thickness or full thickness	Meshed SSG		Difference from meshed SSG						
			Meshed SSG + ReCell		ReCell alone		ReCell + biosynth. dressing		
36. What are the differences in consumables used between treatment options? E.g. autografts are stapled and require a meshing device, but ReCell does not require either.									
Dressing changes	37. How many days are there between surgery and the first dressing change/wound assessment?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	38. How frequent are dressing changes for the burn wound?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	39. What proportion of patients have their first few dressing changes in theatre under GA? a. For how long are these patients likely to require a GA for dressing changes?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	b. What staff are required in theatre?								
	c. How long does this take in theatre?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	40. For patients who only require simple analgesia for dressing change on the burns ward: a. What analgesia is used?								
	b. What staff are required?								



Group B: 10% TBSA deep partial thickness or full thickness	Meshed SSG		Difference from meshed SSG						
			Meshed SSG + ReCell		ReCell alone		ReCell + biosynth. dressing		
	Avg	Range	Avg	Range	Avg	Range	Avg	Range	
c. How long will this take?	Avg	Range	Avg	Range	Avg	Range	Avg	Range	
41. What dressings are changed for the burn wound?									
42. How frequent are dressing changes for the donor site?	Avg	Range	Avg	Range	Avg	Range	Avg	Range	
43. What dressings are changed for the donor site?									
Discharge/ Length of stay	44. What proportion of patients are discharged to outpatient treatment following the first dressing change?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	45. What is the total length of stay in hospital for this patient population (days)?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	46. Are there any substantial differences between dressing changes on the ward and those in outpatients (e.g. time required, number/type of staff, analgesia, frequency or dressing type)? Please comment.								
Healing and retreatment	47. For patients with uncomplicated wound healing how long do you expect the burn wound to take to heal (from initial surgical treatment to >95% healing, no further dressings required)?	Avg	Range	Avg	Range	Avg	Range	Avg	Range



Group B: 10% TBSA deep partial thickness or full thickness	Meshed SSG		Difference from meshed SSG					
			Meshed SSG + ReCell		ReCell alone		ReCell + biosynth. dressing	
48. For patients with uncomplicated wound healing how long do you expect the donor site to take to heal?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
49. What proportion of patients would require additional surgical intervention (e.g. regrafting) due to poor healing?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
50. At what point is the decision taken to provide surgical intervention (days post-surgery)?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
51. What are the options for secondary surgical intervention? (Is this affected by the initial treatment?)								
52. How does the second procedure differ from the first (e.g. duration, size of graft, materials used, staff)?								
53. How long would you expect the wound to take to heal following secondary surgical treatment (days)?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
54. What proportion of patients do you expect to develop hypertrophic scars?	Avg	Range	Avg	Range	Avg	Range	Avg	Range

Use of ReCell	55. Are there specific circumstances under which you would or would not use ReCell, other than standard contraindications (e.g. not on burns smaller than 3% TBSA, not on face burns)?	
	56. Does the availability of ReCell affect the need for donor sites or their size, e.g. would you use a higher mesh ratio if you have the use of ReCell? If so, can you quantify this?	



	57. Does the use of ReCell affect analgesia requirements for background pain?	
Long term scar outcomes	58. Does the use of ReCell improve the appearance and/or function of the eventual scar? If so, how: a. pigmentation outcomes? b. incidence of poor scarring? c. use of conservative scar treatments (creams, compression, steroid injections)? d. requirement for surgical scar revisions?	
	59. Does the use of ReCell affect any other long term outcomes? (E.g. psychological, need for occupational therapy, need for social services support.) If so, how?	
Source	60. Are your answers in general based on personal recall of experience, access to collected data (e.g. local audit or national databases) or other?	

Any additional comments, e.g. on the treatment of this type of patient, on the questions asked or on the use of ReCell.

Group C patients: large, 40% TBSA, deep dermal/partial thickness or full thickness burns that are expected to require wide meshed split thickness skin grafts (SSG)

The burn does not involve complex areas (e.g. face, hands, genitals) and has no obvious infection. Patients’ length of stay and care is dependent only on their skin burn wounds, i.e. there are no other injuries (e.g. inhalational, fractures), difficult social circumstances or large distance to home that preclude discharge.

Assumptions:

- Patients go to theatre within 2 days (48 hours) post injury.
- All surgical treatments require the same wound preparation.



- Patients have dressing changes under GA and remain on HDU for the same length of time and are then transferred onto the burns ward when dressing changes require simple analgesia.
- Any patient requiring later surgical intervention for unhealed burns will only require one instance of treatment to achieve healing.

Treatment options:

The burn wound can be treated in one of several ways:

- wide meshed split thickness autograft (SSG),
- wide meshed split thickness autograft (SSG) plus ReCell,
- wide meshed autograft plus cultured cells,
- ReCell plus conventional dressing (e.g. Telfa),
- ReCell plus biosynthetic dressing (e.g. Biobrane).

61. Are any of these treatment options nonsensical (e.g. you would not use ReCell alone in this patient population)?

62. Are any of the assumptions nonsensical?

Group C: 40% TBSA deep partial thickness or full thickness		Wide meshed SSG		Difference from wide meshed SSG							
				Wide meshed SSG + ReCell		Wide meshed SSG + cultured cells		ReCell alone		ReCell + biosynth. dressing	
		Avg	Range	Avg	Range	Avg	Range	Avg	Range	Avg	Range
Initial surgical treatment	63. How many operations do you expect to need for the initial surgical treatment?	Avg	Range	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	64. What would you expect the overall surgery time to be (sum of all procedure times)?	Avg	Range	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	65. How many & what staff would you expect to need in theatre? (E.g. consultant surgeon, trainee surgeon, anaesthetic staff, ODA/ODP, scrub nurse, other.)										



Group C: 40% TBSA deep partial thickness or full thickness	Wide meshed SSG		Difference from wide meshed SSG								
			Wide meshed SSG + ReCell		Wide meshed SSG + cultured cells		ReCell alone		ReCell + biosynth. dressing		
66. How is the burn wound dressed? a. Primary (contact) dressing b. Secondary (protective) dressing c. Untreated burn area (e.g. temporary dressing)											
67. What mesh ratio is used?	Avg	Range	Avg	Range	Avg	Range	Avg	Range	Avg	Range	Range
68. How large is the donor site (cm ²)?	Avg	Range	Avg	Range	Avg	Range	Avg	Range	Avg	Range	Range
69. How is the donor site dressed?											
70. What is the typical delay between surgical treatments?	Avg	Range	Avg	Range	Avg	Range	Avg	Range	Avg	Range	Range
71. What determines the time period between operations (not including theatre/staff availability)?											
72. What are the differences in consumables used between treatment options (excluding the ReCell kits)? E.g. autografts are stapled and require a meshing device, but ReCell does not require either.											
Dressing 73. How frequent are dressing changes for the burn wound?	Avg	Range	Avg	Range	Avg	Range	Avg	Range	Avg	Range	Range



Group C: 40% TBSA deep partial thickness or full thickness changes		Wide meshed SSG		Difference from wide meshed SSG							
				Wide meshed SSG + ReCell		Wide meshed SSG + cultured cells		ReCell alone		ReCell + biosynth. dressing	
		Avg	Range	Avg	Range	Avg	Range	Avg	Range	Avg	Range
74.	For how long are patients likely to require an HDU stay/GA for dressing changes?										
a.	What staff are required in theatre?										
b.	How long do dressing changes take in theatre?										
c.	What dressings are changed for the burn wound?										
75.	How frequent are dressing changes for the donor site?										
76.	What dressings are changed for the donor site?										
77.	When patients move onto simple analgesia for dressing changes on the burns ward:										
a.	What analgesia is used?										
b.	What staff are required?										
c.	How long will the procedure take?										
d.	What dressings are changed for the burn wound?										
e.	What dressings are changed for the donor site?										
Length of stay	78. What is the total length of stay in hospital (days)?										



Group C: 40% TBSA deep partial thickness or full thickness		Wide meshed SSG		Difference from wide meshed SSG							
				Wide meshed SSG + ReCell		Wide meshed SSG + cultured cells		ReCell alone		ReCell + biosynth. dressing	
Healing and retreatment	79. For patients with uncomplicated wound healing how long do you expect the burn wound to take to heal (from initial surgical treatment to >95% healing, no further dressings required)?	Avg	Range	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	80. For patients with uncomplicated wound healing how long do you expect the donor site to take to heal?	Avg	Range	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	81. What proportion of patients would require secondary surgical intervention (e.g. re-grafting) due to poor healing?	Avg	Range	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	82. At what point is the decision taken to provide secondary surgical intervention (days since initial surgery)?	Avg	Range	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	83. What are the options for secondary surgical intervention? (Is this affected by the initial treatment?)										
	84. How does the second intervention differ from the first (e.g. duration, size of graft, materials used, staff)?										
	85. How long would you expect the wound to take to heal following secondary surgical treatment?	Avg	Range	Avg	Range	Avg	Range	Avg	Range	Avg	Range



Group C: 40% TBSA deep partial thickness or full thickness	Wide meshed SSG		Difference from wide meshed SSG							
			Wide meshed SSG + ReCell		Wide meshed SSG + cultured cells		ReCell alone		ReCell + biosynth. dressing	
	Avg	Range	Avg	Range	Avg	Range	Avg	Range	Avg	Range
86. What proportion of patients do you expect to develop hypertrophic scars?										

Use of cells	87. What is the upper TBSA limit above which you would not use ReCell on the burn wound?	
	88. What is the lower TBSA limit below which you would not use cultured cells?	
	89. Does the availability of ReCell affect the need for donor sites or their size, e.g. would you use a higher mesh ratio if you have the use of ReCell? If so, can you quantify this?	
	90. How do you use ReCell in these patients? (E.g. primarily over the meshed grafts, primarily on the graft donor sites, only on the donor sites if there is sufficient fluid left, only for certain mesh ratios?)	
	91. Does the use of ReCell affect analgesia requirements for background pain?	
	92. Do you consider that the use of ReCell may have an effect on survival in this patient population?	
Long term scar outcomes	93. Does the use of ReCell improve the appearance and/or function of the eventual scar? If so, how: <ul style="list-style-type: none"> a. pigmentation outcomes? b. incidence of poor scarring? c. use of conservative scar treatments (creams, compression, steroid injections)? d. requirement for surgical scar revisions? 	
	94. Does the use of ReCell affect any other long term outcomes? (E.g. psychological, need for occupational therapy, need for social services support.) If so, how?	



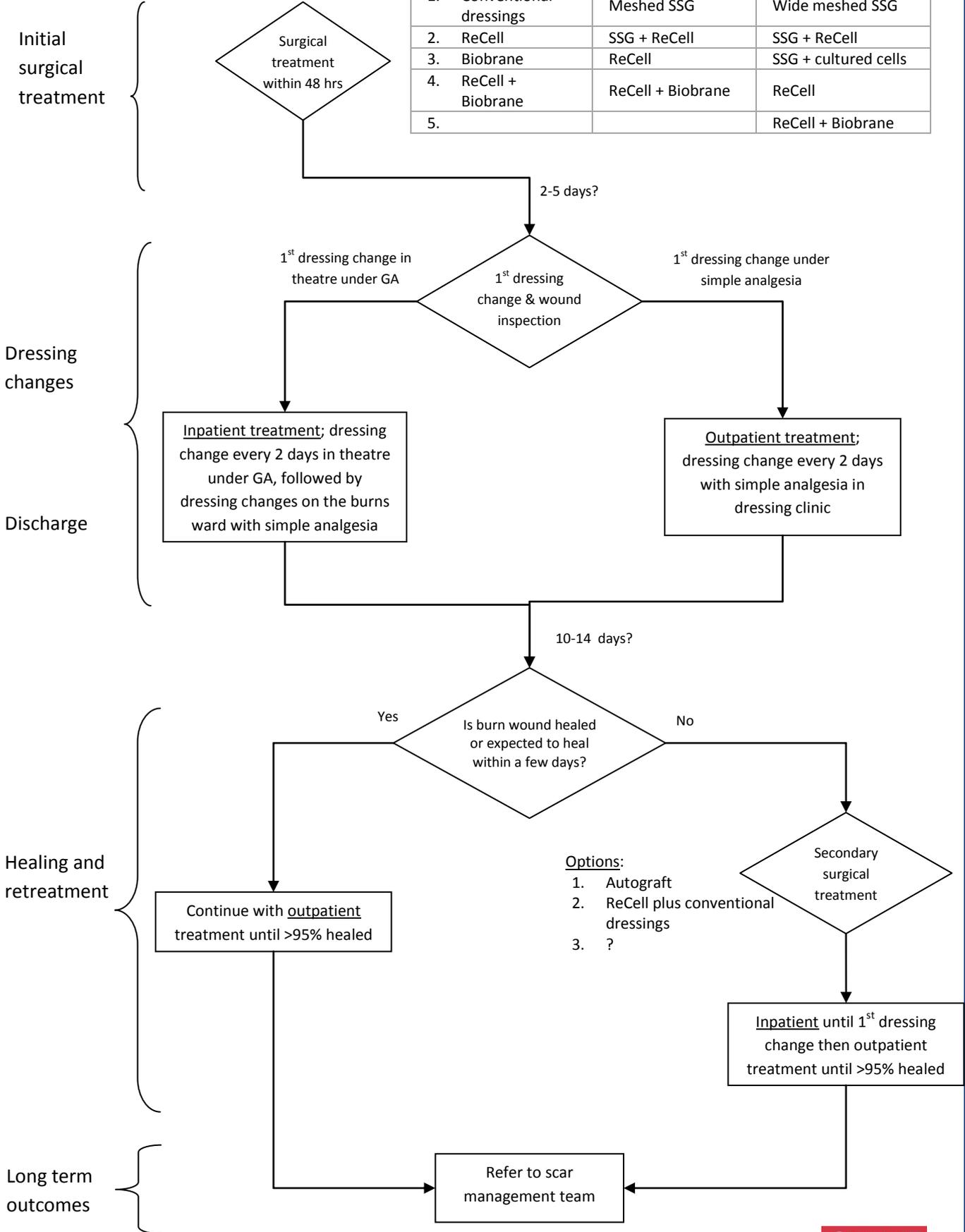
Source	95. Are your answers in general based on personal recall of experience, access to collected data (e.g. local audit or national databases) or other?	
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Any additional comments, e.g. on the treatment of this type of patient, on the questions asked or on the use of ReCell.

6 Appendix 2 – generic patient pathway

Generic patient pathway for admitted skin burns care

Options:		
1. Conventional dressings	Meshed SSG	Wide meshed SSG
2. ReCell	SSG + ReCell	SSG + ReCell
3. Biobrane	ReCell	SSG + cultured cells
4. ReCell + Biobrane	ReCell + Biobrane	ReCell
5.		ReCell + Biobrane



7 Appendix 3 – expert advisers

Name	Hospital
Jackie Edwards	Wythenshawe Hospital, Manchester
Sian Falder	Alder Hey Hospital, Liverpool
Ian James	Whiston Hospital, Liverpool
Ian Mackie	Frenchay Hospital / Bristol Childrens Hospital
Naiem Moiemem	Queen Elizabeth Hospital, Birmingham
Ciaran O'Boyle	Queens Medical Centre / City Hospital, Nottingham
David Ralston	Sheffield Children's Hospital/Northern General Hospital
Mamta Shah	Royal Manchester Children's Hospital
Paul Stephens	Stoke Mandeville Hospital, Aylesbury
Michael Tyler	Stoke Mandeville Hospital, Aylesbury
Yvonne Wilson	Birmingham Children's Hospital



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Caerdydd a'r Fro
Cardiff and Vale
University Health Board



External Assessment Centre Project Specification Form	
Project Number	MT205
Evaluation title	The ReCell Spray-On Skin system for treating skin loss, scarring and depigmentation after burn injury
Synopsis of the technical issue	<p>At its meeting on 21 November 2013, having considered the information in the sponsor's submission, assessment report and assessment report overview, and having received advice from two clinical experts, the Medical Technologies Advisory Committee requested further information before making provisional recommendations for the ReCell Spray-On Skin System.</p> <p>The Committee was disappointed with the lack of economic modelling for patients with full thickness or deep partial thickness burns. It heard from clinical experts that the largest potential value of the ReCell Spray-On Skin System could be for use with wide mesh skin grafting to treat full thickness or deep partial thickness burns. The Committee requested that an economic model for these burns be developed to aid their decision-making in developing recommendations on this technology.</p> <p>The Committee recognised that published data to produce a cost model for patients with full thickness or deep partial thickness burns, which require grafting, are not available. It considered that model parameters could be based on expert opinion similar to the approach used for the sponsor submitted partial thickness burns model but it recommended that a broad range of suitable experts working in the NHS are used. The Committee noted that it is possible that some relevant centre-based audit data may be identified if more experts are contacted</p> <p>The Committee also questioned some of the parameters in the economic model</p>

	<p>for the partial thickness burns patient population, particularly those parameters (length of in-patient stay, time to epithelialisation and requirement for a skin graft) which were based on limited clinical opinion. It requested that broader clinical opinion and any additional data available be collected to confirm that the values for the model parameters were appropriate.</p> <p>The Committee also considered the potential impact of the use on ReCell on improving skin colour match in burns scars. The Committee noted a difference of opinion from the experts about the generalisability of the existing evidence in patients with hypopigmented scars and vitiligo lesions to burns patients. The Committee was aware that the skin colour match in scars is an important patient outcome and agreed that it would like further information from a broad range of experts about this issue.</p>
<p>Objectives for EAC of additional work package</p>	<p>1. Identification of group of experts to contribute to additional work</p> <ul style="list-style-type: none"> • To determine the best method of contacting a wider selection of experts to inform the additional work. These experts should be ratified by their specialist societies using NICE’s published processes (Process Guide, section 3.7.2) • To identify and seek agreement to participate from, an appropriate group of experts to provide information for the additional work on the ReCell Spray-on skin evaluation. <p>2. Economic model for full thickness or deep partial thickness burns which require grafting</p>

	<ul style="list-style-type: none">• To use a suitable process to collect information from experts to populate the economic model. The topic lead team (NICE technical adviser, Committee member, Expert Advisers) should be involved in the development of questions for this process. If possible the uncertainty associated with expert judgments should be characterized so this can be reflected in the economic model.• To collect the information from the identified group of experts. This may involve a questionnaire and follow-up telephone interviews with some experts.• To identify any additional data from local audits or national databases (such as http://www.ibidb.org/) that could be used to inform the model parameters.• To carry out an economic analysis of the cost impact of the ReCell Spray-On Skin System for treating burns which require grafting. This should be considered as two subgroups:<ul style="list-style-type: none">a. <u>Large area burns which are judged to need wide mesh grafting</u> These large area burns are likely to involve multiple rounds of surgery and grafting, with ITU or HDU care and with multiple organ support. Such burns are often life-threatening and survival depends
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on wound closure.

- ◇ Population: Patients with large area full thickness or deep partial thickness burns where wide mesh grafting is needed.
- ◇ Intervention: Skin mesh graft in combination with ReCell Spray-on skin and possible use of ReCell Spray-on skin at donor site.
- ◇ Comparator: Skin mesh graft and current donor site treatment
- ◇ Consider use of cultured cells with skin mesh graft if available.

b. Full thickness or deep partial thickness burns which are judged to need skin grafting

These burns are anticipated to only require 1 round of surgery and patients would be cared for on a general ward with no organ support.

These burns are generally not life threatening.

- ◇ Population: Patients with full thickness or deep partial thickness burns where grafting is needed.
- ◇ Intervention: ReCell Spray-on skin alone
ReCell Spray-on skin plus skin graft
- ◇ Comparator: Skin graft alone

The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared.

3. Hypopigmentation and use of ReCell Spray-on skin

	<ul style="list-style-type: none"> • Define questions about use of ReCell Spray-on skin to improve skin colour match in scars. The experts from the lead team should be involved in the development of questions. • Collect information from experts group and analyse responses. • Review any relevant evidence including any patient reported outcomes on the acceptability of scar appearance. <p>4. Parameters in sponsor’s economic model for patients with partial thickness burns (with any revisions made by the EAC described in the assessment report)</p> <ul style="list-style-type: none"> • To confirm using expert advice or any relevant data whether the model parameters (length of in-patient stay, time to epithelialisation and requirement for a skin graft) have been accurately estimated in the sponsor’s submission. • If more appropriate values are identified the model should be updated and re-run.
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External Assessment Centre Project Administration Form	
Project Number	MT205

EAC Project Leader(s)	Sue Peirce and Grace Carolan-Rees
Date form sent to EAC	16 th December 2013
NICE contacts <ul style="list-style-type: none"> • Associate Director • Technical Lead • Technical Adviser • Project manager 	Mark Campbell Caroline Hall Bernice Dillon Phil Pugh
Timelines:	
<ul style="list-style-type: none"> • Start date 	17 th December 2013
<ul style="list-style-type: none"> • Date for delivery of draft report 	To be arranged
<ul style="list-style-type: none"> • Date for delivery of report to Institute 	3 rd March 2014 The EAC's report will be presented to the Committee without any editing or summarising by NICE and so should be prepared with that in mind, and with appropriate cross-referencing to the submission, AR and ARO. The project objectives should be included as an Appendix.
<ul style="list-style-type: none"> • Date of Committee meeting for presentation of report 	20 th March 2014
<ul style="list-style-type: none"> • Arrangments for EAC/NICE liaison 	By regular teleconference, initially weekly

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Assessment report overview

The ReCell Spray-On Skin system for treating skin loss, scarring and depigmentation after burn injury

This assessment report overview has been prepared by the Medical Technologies Evaluation Programme team to highlight the significant findings of the External Assessment Centre (EAC) report. It includes key features of the evidence base and the cost analysis, any additional analysis carried out, and additional information, uncertainties and key issues the Committee may wish to discuss. It should be read along with the sponsor's submission of evidence and with the EAC report. The overview forms part of the information received by the Medical Technologies Advisory Committee when it develops its recommendations on the technology.

Some potential key issues for consideration by the Committee are described in section 6, following the summaries of the clinical and cost evidence.

This report contains information that has been supplied in confidence and will be redacted before publication. This information is highlighted in [REDACTED].

This overview also contains:

- Appendix A: Sources of evidence
- Appendix B: Comments from professional bodies
- Appendix C: Comments from patient organisations
- Appendix D: External Assessment Centre correspondence
- Appendix E: Sponsor's factual check of the assessment report and the External Assessment Centre's responses

1 The technology

The ReCell Spray-On Skin (Avita Medical Ltd) is a rapid autologous cell harvesting, processing and delivery system for treating skin loss and preventing scarring and depigmentation in adults and children with burns. The ReCell Spray-On Skin is prepared by taking a thin piece of split-thickness skin to harvest keratinocytes, melanocytes, fibroblasts and Langerhans cells. The cells are processed into a suspension, and delivered to the treatment area, using proprietary preparation and 'spray-on' processes. Cells from the suspension are able to rapidly proliferate and migrate in the wound bed. The regenerative nature of these skin cells is intended to promote the growth of healthy skin to facilitate rapid healing. It takes approximately 20–30 minutes in total to collect the tissue and prepare and apply the cell suspension. The procedure is designed to be carried out by clinicians, without input from specialised laboratory staff.

2 Proposed use of the technology

2.1 *Disease or condition*

Burns are relatively common and often extremely painful. Although most burns are minor, serious burns can result in disabling or disfiguring scarring, amputation or death. Recovery from a serious burn injury is associated with emotional and physical challenges and can have a significant effect on quality of life. A study of people hospitalised for burns found that around half changed job status as a result of their injury (Weichman and Patterson 2004). Burns can also lead to increased fear, grief, anxiety and depression and in some cases, post-traumatic stress disorder. Scarring can lead to negative body image, feelings of social isolation and social stigma.

The majority of burn injuries are caused by heat, with around 5% caused by chemical injury or electrocution. The main causes of severe burn injury are flame burns and liquid scalds.

2.2 Patient group

The ReCell Spray-On Skin can be in adults or children to treat partial thickness burns for which mesh grafts are not needed, or large area burns for which mesh grafts are needed. The ReCell Spray-On Skin should be used by burns experts in burns units or centres as suggested in the decision problem in the scope.

Around 250,000 people in the UK seek medical attention for burns each year. Of these, around 175,000 attend accident and emergency departments and the UK admission rate is 0.29 per 1000 cases of burns or smoke inhalation. In England in 2011/12 there were 12,213 hospital admissions for burns and corrosions (chemical burns), of which 9043 were emergency admissions. The average number of burns-related deaths in the UK each year is 300.

2.3 Current management

The treatment of burns can be considered in 2 phases: acute and reconstructive. The acute phase is the initial management of the injury with the intention that burn wound healing will occur with minimal scarring and physical limitation. The reconstructive phase aims to improve the functional or visual impact of scarring, usually by surgical means, and may be done months or years after the initial injury.

The first step in managing a burn injury is to assess the depth of the burn, the proportion of the body area involved and the site of injury. Burn depth is classified according to the level of skin or tissue affected. Epidermal and superficial dermal wounds tend to heal without scarring or surgical intervention within 21 days. Deep dermal or deep partial-thickness (where epidermis and dermis are both damaged) and full-thickness burns (epidermis, dermis and subcutis are damaged) may need surgical excision (to remove the burnt skin and tissues) and skin grafting to ensure rapid healing, to minimise scarring and reduce complications. It is usual for surgical excision to take place within a day or 2 of admission. For mixed-depth, partial-thickness scalds or burns, decision making to graft normally occurs over 14-21 days unless the

patient's condition deteriorates before this. If wounds are still unhealed after 14–21 days, skin grafts can be used to achieve a better cosmetic result.

Full-thickness burns more than 1 cm in diameter need skin grafts because the regenerative components of the skin have been lost. Healing can occur only from the edges of the wound; without a graft the skin contracts, leading to a poor cosmetic outcome and reduced mobility. Deep dermal burns are unlikely to heal within 3 weeks and will therefore often need grafting.

Skin grafts may be classified as partial or full-thickness grafts, depending on how much of the dermis is harvested by the surgeon. The clinical 'gold standard' for skin grafting is an autologous split-thickness graft taken from an area of unburnt skin. Grafts should ideally be taken from donor sites adjacent to the injury to improve the match with the surrounding skin. The donor site is itself a wound and needs treatment to ensure healing. If large grafts are needed for extensive wounds the donated skin can be perforated (or meshed) to increase the surface area. The pattern of meshing can be visible after healing, so sheet grafting is preferable to improve the cosmetic result.

Allografting (using skin from another person, often after death) and xenografting (using skin from animals) can also be used for temporary wound closure but these will ultimately be rejected by the body. Other alternatives to autologous grafts for deep partial-thickness and full-thickness wounds include artificial skin products.

2.4 *Proposed management with new technology*

For this assessment, the aim of the ReCell Spray-On Skin system is to treat partial thickness burns (for which a mesh grafting is not needed) and large area burns (for which mesh grafting may be needed) in adults and children in burns centres or units. Introducing this technology would not involve a significant change to current practice.

2.5 *Equality issues*

Two potential issues were identified at scoping:

- Skin grafting in people with darker skin can result in a poor colour match in the grafted area. The sponsor claimed that treatment with ReCell Spray-On Skin could result in better matching of skin colour. The evidence for this claim presented by the sponsor was in patients with hypopigmented scars and vitiligo lesions. However, the EAC considered that outcomes in these populations could not be extrapolated to patients with acute burns (see section 4.1). None of the included burns studies reported population ethnicity or any difference in outcomes according to skin colour. One expert adviser indicated that ReCell Spray-On Skin appears to produce better pigmentation outcomes than would otherwise have been expected (including in patients with darker skin).
- The trypsin enzyme used to disaggregate the skin cells from the biopsy during the ReCell process is derived from pigs. This means that the treatment may be unacceptable to people whose religious or cultural beliefs forbid contact with porcine material. The sponsor noted that the porcine origin of trypsin is well recognised and that Biobrane (a biosynthetic dressing which is currently used in the NHS to dress some burns) also contains material of porcine origin. Expert advice to the EAC indicated some variation in practice; either all patients are routinely informed about the nature of the product or only those patients who are suspected to object.

3 Decision problem

3.1 Sponsor's claimed benefits

The benefits to patients claimed by the sponsor are shorter wound healing time at the recipient site, leading to:

- improved aesthetic result with a lower likelihood of scarring of the burn wound and better match of skin colour
- repopulation of melanocytes to reduce hypopigmentation in healed wounds
- reduced dressing change frequency (weekly rather than daily)
- less need for dressing changes under anaesthetic
- a reduction in skin graft donor site size and depth

- fewer complications, reduced morbidity and shorter healing time at the donor site.

The benefits to the health system claimed by the sponsor are reductions in:

- length of stay in hospital, because weekly rather than daily dressing changes allow earlier discharge and outpatient management, thus reducing the costs of care
- re-dressings under anaesthetic, again reducing the costs of care
- the need for external technical laboratory support
- the likelihood of readmission for corrective surgery, because of improved aesthetic results.

The claimed benefits, together with the Committee's selection considerations, were used to develop the scope for the evaluation. Table 1 is a summary of the decision problem, on which the sponsor's submission was based. The decision problem generally contains a comprehensive list of the outcomes by which the technology's benefits could be realised. However the sponsor may choose to not submit evidence on all outcomes, either because none exists, or because there is no relevant evidence.

The sponsor did not vary the outcomes in the decision problem but the EAC highlighted an extra outcome included in the sponsor's submission: 'Graft loss or graft take following initial surgical and requirement for subsequent skin grafting' (page 16 of the assessment report).

Table 1 Summary of decision problem

	Scope issued by NICE
Population	Adults or children treated in burns units or centres for: <ul style="list-style-type: none"> • partial thickness burns, including scalds caused by hot water, for which mesh grafting is not needed • large area burns; full thickness or deep partial thickness burns, including those for which mesh grafting is needed
Intervention	For partial thickness burns, including scalds caused by hot water: <ul style="list-style-type: none"> • ReCell Spray-On Skin alone, or in combination with biosynthetic or standard dressings For large area burns and full or deep partial thickness burns for which mesh grafting is needed: <ul style="list-style-type: none"> • skin mesh graft in combination with ReCell Spray-On Skin
Comparator(s)	For partial thickness burns, including scalds caused by hot water: <ul style="list-style-type: none"> • Biosynthetic dressings (e.g. Biobrane) • Standard dressings For large area burns; full or deep partial thickness burns for which mesh grafting is needed: <ul style="list-style-type: none"> • Skin mesh graft alone • Skin mesh graft plus biosynthetic dressing
Outcomes (full details in scope)	The outcome measures to consider: <ul style="list-style-type: none"> • speed of healing • length of stay • degree of scarring • degree of pigmentation • device-related adverse events, such as wound infection rates
Special considerations, including issues related to equality	Skin grafting in people with darker skin can result in a poor colour match in the grafted area. The ReCell Spray-On Skin system may result in better colour matching of the resulting skin. The trypsin enzyme used to disaggregate the skin cells from the biopsy during the ReCell process is derived from pigs. This means that the treatment may be unacceptable to people whose religious or cultural beliefs forbid contact with porcine material.

4 The evidence

4.1 *Summary of evidence of clinical benefit*

The sponsor's search identified 18 published references and 1 unpublished abstract relevant to the ReCell Spray-On Skin system. The sponsor excluded 7 references and presented the remaining 3 peer-reviewed journal papers and 8 conference abstracts. The EAC considered 2 of the conference abstracts (Echlin 2012b; Palombo 2012) to be outside the scope and identified an

additional 9 conference abstracts (of which 2 were unavailable and 5 contained data that overlapped with other references presented by the sponsor; section 3.3 page 21 of the assessment report). The EAC noted that the 9 additional references were identified by duplicating the sponsor's search strategy and that the sponsor provided no reasons for why they were excluded.

The sponsor also identified and presented 5 published studies in support of the degree of pigmentation outcome specified in the decision problem. The EAC considered all 5 to be outside the scope because the patient populations were people with scars or vitiligo and did not include people with burns. The EAC decided, on the basis of clinical expert advice, that evidence on the effect of the ReCell Spray-On Skin system in wounds created by dermabrasion and hypopigmentation lesions was not generalisable to the treatment of acute burns wounds.

Summaries of studies

A brief description of the relevant ReCell studies is given below and in table 2 (studies included by the sponsor) and table 3 (additional studies identified by the EAC). Full details of the methodologies and outcomes are provided in section 3.4 and 3.5 of the assessment report (pages 25–40). The EAC identified overlaps in the patient populations reported in multiple studies and contacted authors to obtain further information. Despite this, there is uncertainty about the degree of overlap between some studies.

Published studies

Full studies

Gravante et al. (2007) conducted a single centre randomised controlled non-inferiority trial in Italy to compare the ReCell Spray-On Skin system with skin grafting, for treating deep partial thickness burns in 82 adults. Aesthetic quality of the scars was measured using the Vancouver scar scale by 2 plastic surgeons, 1 of whom was blinded to the procedure. The functional quality of the scar was measured, based on the development of contractures (an area of skin that has undergone excessive scarring and can develop into

hypertrophic scars), after 1 month. Time to complete epithelialisation was 13 ± 2 days (mean \pm standard deviation) for the ReCell group and 12 ± 2 days for the comparator group (difference not significant). Despite being part of the study design, Vancouver Scar Scale values were not reported but were not different between the groups according to the judgment of 2 plastic surgeons. In the ReCell group 12 patients developed at least 1 contracture, as did 15 in the comparator group (difference not statistically significant). Postoperative pain in the ReCell group was statistically significantly reduced compared with pain in the comparator group ($p=0.03$). Postoperative analgesia was the same in both groups, although patients in the comparator group 'complained of an additional painful site (the area of harvesting)'. Procedure time (unreported) was significantly longer for the ReCell group than the comparator ($p<0.001$) group. The donor area harvested for the ReCell group was significantly smaller than that for the comparator group ($p<0.001$). A second procedure was needed for 7 patients in the ReCell group and 6 in the comparator group.

Park et al. (2013) carried out a retrospective multivariate analysis in Australia. The study included 767 patients who were admitted to the burns centre between January 2004 and December 2011 and who needed skin grafting or a skin replacement procedure. Patients were divided into 3 groups: the ReCell Spray-On Skin system alone, the ReCell Spray-On Skin system plus standard skin graft, or standard skin graft alone. The aim of the study was to determine whether infection, graft loss and length of stay were related to surgical intervention for burns. The study indicated that the type of surgical intervention did not influence the likelihood of the patient having a burn wound infection. The ReCell Spray-On Skin system alone was associated with a reduction in length of stay compared with standard skin graft alone (odds ratio [95% CI] 0.7 [0.57–0.82], $p<0.01$) but the ReCell Spray-On Skin system plus standard skin graft was not (0.98 [0.88–1.10], $p=0.85$). The authors concluded that the ReCell Spray-On Skin system reduced patients' length of stay by 30% ($p<0.01$) compared with standard skin graft. The EAC noted that the authors did state that the reduction of length of stay demonstrated by the ReCell Spray-On Skin system should be carefully interpreted because wound depth treated and surgery timing differed between the ReCell group and the

standard skin graft group. Burn depth and total burn surface area were taken into account to calculate the severity of the burn and the authors indicated that the reduction in donor skin harvesting for the ReCell technique may have reduced the length of stay.

Wood et al. (2012) carried out a 3-armed randomised controlled pilot study at a burn centre in western Australia, evaluating the use of the ReCell Spray-On Skin system plus Biobrane, Biobrane alone, and local standard treatment dressings every 2–3 days with definitive surgery at 10–14 days post injury) in 13 children over a 12-month period. The aim of the study was to investigate using early interventions to prevent the need for surgery. None of the patients in the ReCell plus Biobrane group needed surgery 10 days after the burn; 1 patient in the Biobrane group needed surgery, and 3 out of 4 patients in the standard treatment group needed surgery. The median length of time for the ReCell group to reach complete healing was similar to the time for the Biobrane group and the median time was longer in the standard treatment group (median [interquartile range] 16.0 [11.5–18.0], 16.0 [14.25–23.0] and 36.5 [18.5–47.7] days respectively; no statistical analysis provided). The patients treated with the ReCell Spray-On Skin system plus Biobrane experienced greater wound healing, based on the outcome ‘speed of healing’ at both 10 and 21 days post burn compared with Biobrane alone and standard treatment (no statistical analysis provided).

Abstracts

Dunne and Rawlins (2012a) observed 40 children in the UK who had 1 of 3 procedures: the ReCell Spray-On Skin system plus Biobrane (mid and deep dermal burns, n=13), Biobrane (superficial dermal burns, n=20) or standard skin graft (full thickness burns, n=7). The aim of the study was to assess average hospital stay, scar appearance, wound healing, donor site morbidity, and analgesic and dressing costs. Hospital stay was shorter in the Biobrane group and the ReCell plus Biobrane group, and scar assessment was good or good to excellent in all groups.

Echlin et al. (2012a) observed 5 patients with mid to deep dermal facial burns (3 scalds and 2 flame burns) in the UK. Four patients were treated with the ReCell Spray-On Skin system plus non-adherent dressings because they were assessed 9–11 days after the burn and deemed unlikely to recover within 3 weeks. One further patient was assessed 23 days after injury and was treated with the ReCell Spray-On Skin system plus allograft dressing. Analgesia needed at the first dressing change and in total was measured. The authors concluded that the ReCell Spray-On Skin system increased the speed of wound healing and decreased the need for standard skin graft and therefore subsequent scar development. As a result, the burns service involved (Chelsea and Westminster) changed its practice to treat these wounds with the ReCell Spray-On Skin system rather than a skin graft.

Rawlins et al. (2011a) compared 15 adults with deep dermal flame burns treated with either the ReCell Spray-On Skin system plus Biobrane (n=5), or standard skin grafting (n=10) 48–72 hours after injury. The mean time to wound healing was 18 days in the ReCell plus Biobrane group and 48 days for the standard skin graft group. Less analgesia was used in the ReCell plus Biobrane group than the standard skin graft group and scar quality was better in the ReCell plus Biobrane group.

Rawlins (2013) observed 26 children with deep dermal burns who were treated with the ReCell Spray-On Skin system (n=11) or standard skin graft (n=15) in an unspecified location. The mean visual analogue scale score was very similar in the 2 groups (3.9; 95% CI 2.8 to 4.9 for ReCell, and CI 3.3 to 4.5 for standard skin graft; p=0.97). Operative time was longer for the ReCell Spray-On Skin system than the standard skin graft cohort (mean 87 minutes compared with 58 minutes; p=0.05) although the total burn surface area was greater for the ReCell group than the standard skin graft group (mean total burn surface area of 6.5% compared with 2.9%; p=0.04).

Unpublished studies



[REDACTED]

Table 2 Summary of clinical evidence (adapted from table 2 and section 3.4 in the assessment report)

Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
Full, peer-reviewed articles					
Gravante et al. (2007)	Randomised controlled trial (Italy)	<ul style="list-style-type: none"> Partial thickness burns <math><320\text{ cm}^2</math> Adult (30–65 years) Sample size 82 	ReCell applied to burn wound and biopsy site vs Mesh SSG	<ul style="list-style-type: none"> Time to complete epithelialisation (days; mean±sd) 13±2 for ReCell, 12±2 for SSG Functional quality of scar (patients with contractures) 12/42 for ReCell, 15/40 for SSG Postoperative pain (VAS) 3.3±1.6 for ReCell, 6.8±1.2 for SSG (p=0.03) Procedure time (mins) 59±4 for ReCell, 20±6 for SSG (p<0.001) Area harvested (cm²) 2.2±1.0 for ReCell, 110±50 for SSG (p<0.001) No intraoperative or postoperative adverse effects were observed 	<ul style="list-style-type: none"> Lack of clarity around the treatment allocation Blinding difficult for some outcomes The accuracy and precision of time to healing may be poor as patients were assessed weekly.

Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
Park et al. (2013)	Retrospective multivariate analysis (Australia)	<ul style="list-style-type: none"> • Burns treated with skin grafting or replacement • All patients • Sample size 767 (770, 3 excluded) 	<p>Two intervention groups</p> <ul style="list-style-type: none"> • ReCell alone • ReCell plus SSG <p>vs</p> <ul style="list-style-type: none"> • SSG 	<ul style="list-style-type: none"> • Presence of post-operative burn wound infection (odds ratio, CI): ReCell vs SSG 0.78 (0.34-3.42); ReCell+SSG vs SSG 1.23 (0.45-4.52) • Graft loss (OR, CI): ReCell vs SSG 0.89 (0.45-2.32) (p<0.09); ReCell+SSG vs SSG 1.56 (0.56-.21)(p=0.67) • Length of stay (OR, CI) ReCell vs SSG 0.7 (0.57-0.82) (p<0.01); ReCell+SSG vs SSG 0.98 (0.88-1.10) (p=0.85) 	<ul style="list-style-type: none"> • Baselines results between intervention groups not provided • Number of patients in each surgical analysis unknown • Co-author is the inventor of ReCell and Director of Avita Medical

Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
Wood et al. (2012)	Three-arm randomised controlled pilot study (Australia)	<ul style="list-style-type: none"> Scalds >2% TBSA, expected to need surgery Paediatric (8 months – 9 years) Sample size 13 	<p>Two intervention groups</p> <ul style="list-style-type: none"> ReCell plus Biobrane Biobrane <p>Vs.</p> <ul style="list-style-type: none"> Standard Care (SC) with silver (Acticoat) and hydrocolloid (Duoderm) dressings on alternate days 	<ul style="list-style-type: none"> Complete wound healing (days; median, IQR) 16.0 (11.5-18.0) for ReCell+Biobrane, 16.0 (14.25–23.0) for Biobrane, 36.5 (18.5–47.7) for SC Wound healing (Visitrak): ReCell+Biobrane, Biobrane and SC after 10days 95%, 83.2%, 71.2% and after 21 days 100%, 97.7% and 90.1% respectively Scar assessment (VSS) for ReCell+Biobrane (VSS 0,3,5,6), Biobrane (VSS 2,3,3,9) and SC (VSS 0,5,6,6) Change in pain (VAS, pre-post randomisation) for ReCell+Biobrane -1.0, Biobrane -2.0 and SC +1.0 Surgery needed at 10 days: Recell +Biobrane 0/5 (0%), Biobrane 1/4 (25%) and SC 3/4 (75%) Number of dressing changes (median, IQR): ReCell+Biobrane 5.0 (4.0-6.0), Biobrane 7.0 (5.5–9.5) and SC 12.5 (8.0-15.0) 	<ul style="list-style-type: none"> Good randomisation was used but this provided small numbers and resulted in differences in the patient demographics. Burn area is only recorded as TBSA with the ReCell plus Biobrane patients having absolute burn areas that were significantly smaller than the other groups There was also discrepancy in the reported number of days for assessment of surgery Accuracy and precision of healing time is unknown The main author Wood is the co-inventor of ReCell and Director of Avita Medical

Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
Abstracts					
Dunne and Rawlins (2012a)	Retrospective review (UK)	<ul style="list-style-type: none"> Scalds of differing depth Paediatric (9 months–15 years) Sample size 40 	<ul style="list-style-type: none"> Biobrane (Superficial dermal) ReCell plus Biobrane (Mid and deep dermal) Early skin grafting (SSG) 	<ul style="list-style-type: none"> Frequency of secondary SSG for ReCell+Biobrane 5/13 (38%), Biobrane 6/20 (30%) and SSG alone 2/7 (29%) Qualitative outcomes included <ul style="list-style-type: none"> hospital stay, scar assessment, wound healing, analgesic and dressing costs 	<ul style="list-style-type: none"> Non-comparative review of patients with different scald depths. The patients were treated 3 different ways therefore can be regarded as 3 different case studies
Echlin et al. (2012a)	Case series (UK)	<ul style="list-style-type: none"> Mid to deep dermal facial burns Age 10 months to 50 years) Sample size 5 	<ul style="list-style-type: none"> Patients that were assessed at 9–11 days post injury and deemed would not heal in 3 weeks were treated with ReCell and non-adherent dressing 	<ul style="list-style-type: none"> Time to healing (days; mean) 	<ul style="list-style-type: none"> 1 patient treated at 23 days There was very little numerical data There was no data on the previous standard of care
Rawlins (2011a)	Comparative pilot study using matched controls (Not reported, probably Australia)	<ul style="list-style-type: none"> Deep dermal burns Adult (17–59 years) Sample size 15 	Intervention <ul style="list-style-type: none"> ReCell plus Biobrane Data from matched controls who received standard skin graft 	<ul style="list-style-type: none"> Length of time to wound healing (days; mean) for ReCell 18 and SSG 48 Qualitative outcomes including <ul style="list-style-type: none"> Analgesia needs Scar assessment at 6 months 	<ul style="list-style-type: none"> Overlap with Rawlins <i>et al.</i> (2011b) and Rawlins (2011a) No report on how the controls were selected

Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
Rawlins (2013)	Unclear if prospective or retrospective, comparative study (Not reported, probably UK)	<ul style="list-style-type: none"> • Deep dermal scalds • Paediatric • Sample size 26 	<ul style="list-style-type: none"> • ReCell vs <ul style="list-style-type: none"> • SSG 	<ul style="list-style-type: none"> • Scar quality (VAS, 95% CI) for ReCell 3.9 (2.8-4.9) and SSG 3.9 (3.3-4.5) (p=0.97) • Operative time (minutes) for ReCell 87 and SSG 58 (p=0.05) • Duration of physiotherapy (days; mean) for ReCell 21 and SSG 40 (p=0.29) 	<ul style="list-style-type: none"> • Overlap with Dunne and Rawlins (2012b) • TBSA was greater in the ReCell group indicating the patient populations differ: TBSA (%) ReCell 6.5, and SSG 2.9 (p=0.04)
Unpublished studies					
Philp et al (2013)		Burns <ul style="list-style-type: none"> • Population unreported • Sample size 10 	<ul style="list-style-type: none"> • ReCell and dressed with Telfa or Biobrane vs <ul style="list-style-type: none"> • SSG harvesting and STDG 	<ul style="list-style-type: none"> • Time to healing for graft and donor site (days; mean) • Patient survival • Scarring 	
Abbreviations: SC - standard care, SSG - standard skin graft, TBSA – total burn surface area; VAS – visual analogue scale, VSS – Vancouver Scar Scale					

Additional studies found by the External Assessment Centre

Dunne and Rawlins (2012b) (overlap with Rawlins 2013) reported early results from the same study as Rawlins (2013).

Dunne and Rawlins (2013) observed 11 children treated with the ReCell Spray-On Skin system plus Biobrane for scalds and 10 adults, 8 of whom were treated with the ReCell Spray-On Skin system plus Biobrane for flame burns and the other 2 were treated for scalds. This is a retrospective review with possible overlap with Rawlins (2013) and Dunne and Rawlins (2012a, 2012b). Outcomes measured included wound coverage, pigmentation, hypertrophic scarring and donor site morbidity. One patient needed a standard skin graft after treatment with the ReCell Spray-On Skin system but early wound coverage and good pigmentation were reported with minimal hypertrophic scarring or donor site morbidity.

Hiller et al. (2013) (possible overlap with Rennekampff et al. 2011) reported outcomes on 5 patients who had partial thickness facial burns and were treated with the ReCell Spray-On Skin. Only narrative outcomes were recorded.

Rawlins (2011a) and Rawlins et al. (2011b) (overlap with Rawlins et al. 2011a) observed 4 patients treated with the ReCell Spray-On Skin system plus Biobrane compared with 10 matched controls who received standard skin grafts. Time to healing, analgesia needs and length of hospital stay were all reduced in the ReCell group compared with standard skin graft group. After 6 months an assessment using the Vancouver Scar Scale demonstrated better results in the ReCell group than in the standard skin graft group.

Rennekampff et al. (2011) (possible overlap with Hiller et al. 2013) reported a case series of 5 patients with facial burns who were treated with the ReCell Spray-On Skin system. Epithelialisation took 7–9 days after surgery and skin pigmentation was slightly reduced compared with skin surrounding the area. There were no hypertrophic scars or severe contractions.

Sood et al. (2009) reported an intra-patient comparative study in 10 patients with partial thickness burns. Patients were treated with the ReCell Spray-On Skin system in 1 area and meshed standard skin grafting in another. Graft take was the main outcome and results showed 100% take at both treatment sites in 8 patients; the other 2 patients had a lower take at the ReCell site (93.6%) than at the standard skin graft site (98.2%).

Table 3 Additional references identified by EAC

Study	Study design (country known)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
Dunne & Rawlins (2012b)	Comparative observational study	Burns Paediatric Sample size 21	<ul style="list-style-type: none"> • ReCell Vs. <ul style="list-style-type: none"> • SSG 	<ul style="list-style-type: none"> • Scar quality (VAS) ReCell 4.6 vs SSG 4.7% (p=0.97) • Operative time (mins) for ReCell 87 vs SSG 64 (p=0.22) • Length of physiotherapy follow-up (days; mean) ReCell 21 vs SSG 25 days (p=0.29) 	<ul style="list-style-type: none"> • Overlap with Rawlins (2013) • Population difference; TBSA (%) ReCell 6.5 vs SSG 4.3 (p=0.22)
Dunne & Rawlins (2013)	Non-comparative observational study	Deep dermal burns All patients Sample size 21	<ul style="list-style-type: none"> • ReCell and Biobrane 	<ul style="list-style-type: none"> • Scar pigmentation • Degree of hypertrophy 	<ul style="list-style-type: none"> • Retrospective review of cases, overlap with Rawlins (2013), Dunne and Rawlins (2012a,b) • No numerical results provided
Hiller et al. (2013)	Case series (Germany)	Partial thickness facial burns <ul style="list-style-type: none"> • Adult (27–81 years) • Sample size 5 	<ul style="list-style-type: none"> • ReCell • ReCell plus grafting 	<ul style="list-style-type: none"> • Author stated 'acceleration in epithelialization and healing time as well as improvement in scar quality'. 	<ul style="list-style-type: none"> • Possible overlap with Rennekamff et al (2011)

Rawlins (2010)	RCT	Scalds Paediatric Sample size unknown	<ul style="list-style-type: none"> Unknown 	<ul style="list-style-type: none"> Unknown 	<ul style="list-style-type: none"> <i>Abstract unobtainable</i>
Rawlins (2011a) Rawlins et al. (2011b)	Comparative pilot study with matched controls	Deep dermal burns to the legs <ul style="list-style-type: none"> Adults (17–59 years) Sample size 14 	<ul style="list-style-type: none"> ReCell plus Biobrane Vs. <ul style="list-style-type: none"> SSG 	<ul style="list-style-type: none"> Time to healing (days) ReCell+Biobrane 18 vs SSG 48 Analgesia needs (mg Tramadol) ReCell+Biobrane 280 mg vs SSG 450 mg Scar assessment (VSS) ReCell+Biobrane 5.3 vs SSG 6.5 	<ul style="list-style-type: none"> Overlap with Rawlins et al. (2011a)
Rawlins (2011b)	Unknown	Scalds Paediatric Sample size unknown	<ul style="list-style-type: none"> Unknown 	<ul style="list-style-type: none"> Unknown 	<ul style="list-style-type: none"> <i>Abstract unobtainable</i>
Rennekampff et al. (2011)	Case series (Germany)	Facial burns (assumed deep partial thickness) <ul style="list-style-type: none"> Population unreported Sample size 5 	<ul style="list-style-type: none"> ReCell 	<ul style="list-style-type: none"> Time to epithelialisation: ReCell 7–9days post-surgery Scar quality and skin pigmentation (qualitative outcome) 	<ul style="list-style-type: none"> Timing of skin grafting not clear
Sood et al. (2009)	Inpatient comparative study	Partial thickness burns <ul style="list-style-type: none"> Population unreported Sample size 10 	<ul style="list-style-type: none"> ReCell Vs. <ul style="list-style-type: none"> Meshed SSG 	<ul style="list-style-type: none"> Graft take (% take) for ReCell 93.6% Vs SSG 98.2% (calculations by EAC) 	<ul style="list-style-type: none"> No description of graft take
Abbreviations: SC - standard care, SSG - standard skin graft, TBSA – total burn surface area; VAS – Visual Analogue Scale VSS – Vancouver Scar Scale					

Conclusions about the clinical evidence

The EAC noted that interpretation of the clinical evidence is limited by inconsistencies between the population, intervention and comparator groups in the studies and those defined in the scope. Despite this, the EAC considered that 2 studies (Gravante et al. 2007; Park et al. 2013) provided robust evidence and concluded that the evidence overall does appear to demonstrate that the ReCell Spray-On Skin system is at least as effective as other current treatments in the care of acute burns within a specialist burns service.

4.2 *Advice from experts and patient organisations*

Expert adviser questionnaires were completed by 5 experts at the briefing note stage (4 of whom also provided advice during the evaluation). No further questionnaires were completed during the evaluation stage. All questionnaires are summarised in appendix B.

NICE's Public Involvement Programme received no response from patient organisations about this technology during the evaluation stage. One patient organisation responded at the initial briefing note stage but the advice received referred to patients outside of the decision problem.

4.3 *Summary of economic evidence*

The sponsor's search was broader than the scope and identified 8 published studies and 1 unpublished audit and cost analysis (Rawlins 2011c). The EAC excluded all the studies identified by the sponsor because they were outside the scope, although it did recognise that the studies contained useful cost information for standard care. The EAC considered that the study by Wood et al. (2012) (not presented by the sponsor as part of its economic evidence) may provide some relevant evidence on costs. But after quality assessment, which showed several limitations (small number of patients, non-UK care pathway, heterogeneous population), the EAC judged that the evidence could not be generalised to support the sponsor's economic case.

De novo analysis

The sponsor submitted a de novo cost analysis model in TreeAge format comparing comparing the ReCell Spray-On Skin system plus conventional dressing, the ReCell Spray-On Skin system plus Biobrane, Biobrane alone, and conventional dressing alone, for treatment of a partial thickness 640 cm² burn. Costs were modelled from an NHS and personal social services perspective. The population included in the model was limited to patients treated for partial thickness burns including scalds, for which mesh grafting was not needed. Patients needing a meshed skin graft were not included in the model.

The model consisted of a decision tree with 4 primary branches: 2 intervention branches (1 ReCell plus Biobrane, 1 ReCell plus conventional dressing (referred to as ReCell alone here); and 2 comparator branches (1 Biobrane and 1 conventional dressing). The model covered a 21-day period. The EAC considered this was an appropriate length of time for an acute episode. The key assumptions are included in section 9.1.5, pages 134–5, of the sponsor's submission and in the costs section below.

Model parameters

In the base-case the sponsor assumed a time to healing of 15 days (based on the mean time to 100% epithelialisation) for the conventional dressing treatment arm. This was based on the median from 3 studies observing conventional topical burn treatments (Caruso et al. 2006; Cuttle et al. 2007; Silverstein et al. 2011), which the EAC judged was appropriate. The sponsor then used a percentage reduction in healing times for the conventional dressings to calculate healing times for the other 3 interventions. The estimated reductions were based on results from Wood et al. (2012) and Ethlin (2012b) and were 30% for Biobrane or ReCell alone and 40% for the combination (see table 4). The EAC were concerned by the use of this data and noted that the only study that that provided any evidence of reduced healing times for ReCell alone was a small case series (Rennekampff et al. 2011). However, the EAC acknowledged that the sponsor took account of the uncertainty in the sensitivity analyses by varying the healing time reductions

for all interventions from 0 to 50%, giving a healing time range of 7.5 to 15 days.

The estimates of the proportion of patients treated as inpatients (page 53 of assessment report) for the different interventions were based on clinical opinion only, although none of the experts could directly answer the questions. The EAC commented that the resulting assumptions are subject to particular uncertainty because of the lack of evidence and direct clinical opinion.

The EAC questioned the value used by the sponsor for the proportion of patients needing a standard skin graft with conventional dressings (30%). It considered that the parameter based on clinical studies (Caruso et al. 2006; Cuttle et al. 2007; Ostlie et al. 2012; Silverstein et al. 2011) may be overestimated because the patient populations were heterogeneous and included severe cases, and clinical opinion suggested a 5–10% standard skin graft rate. The sponsor used clinical opinion to inform this parameter for the other interventions (table 12, page 154 of the assessment report). The EAC noted that the sponsor's values (see table 4) seemed to be higher than those suggested by clinical experts but that there was agreement between experts that the ReCell Spray-On Skin system alone and in combination with Biobrane reduced the number of patients needing a standard skin graft compared with Biobrane alone.

Table 4 Parameters used by sponsor in the model

	Proportion of patients treated as inpatients	Proportion of patients progressing to standard skin graft	Healing time
Conventional dressing	50%	30%	15 days
ReCell	25%	10%	10.5 days
Biobrane	25%	30%	10.5 days
ReCell plus Biobrane	25%	10%	9 days

Costs in the model

The costs included in the de novo analysis are described on pages 55–7 of the assessment report. The EAC noted that the sponsor did not include NHS reference costs as input data or for validating the model.

The cost of each treatment in the model was based on the technology costs and hospital costs; this included staff and dressing costs, together with theatre and bed costs if needed. The general hospital costs in the model were based on data from an unpublished cost analysis ([REDACTED]). In the base case for a partial thickness burn treated with a conventional dressing, costs per patient varied from £4291 to £14,863 depending on the treatment options received, that is inpatient or outpatient care and graft or no graft needed. Taking into account the proportions of patients in each treatment arm, the average cost per patient was £9543 (including hospital costs of £8422 and technology costs of £1121). If the ReCell Spray-On Skin system plus Biobrane were used for treating a partial thickness burn the costs varied from £6082 to £17,082, with an average cost per patient of £7787 (including hospital costs of £5652 and technology costs of £2135). Figure 1 illustrates the overall costs for all the possible treatment pathways in the model and the average patient cost for each intervention.

The EAC highlighted several concerns about the costs used in the model for secondary dressing of wounds. It considered there was uncertainty as to whether the

[REDACTED]

[REDACTED]

[REDACTED]

The cost of secondary dressings was also an area of uncertainty, with little consensus among experts about whether general anaesthesia was needed when changing dressings. Despite initial concerns, the EAC was able to verify the costs used by using an alternative method to derive them (table 13, page 56 in the assessment report).

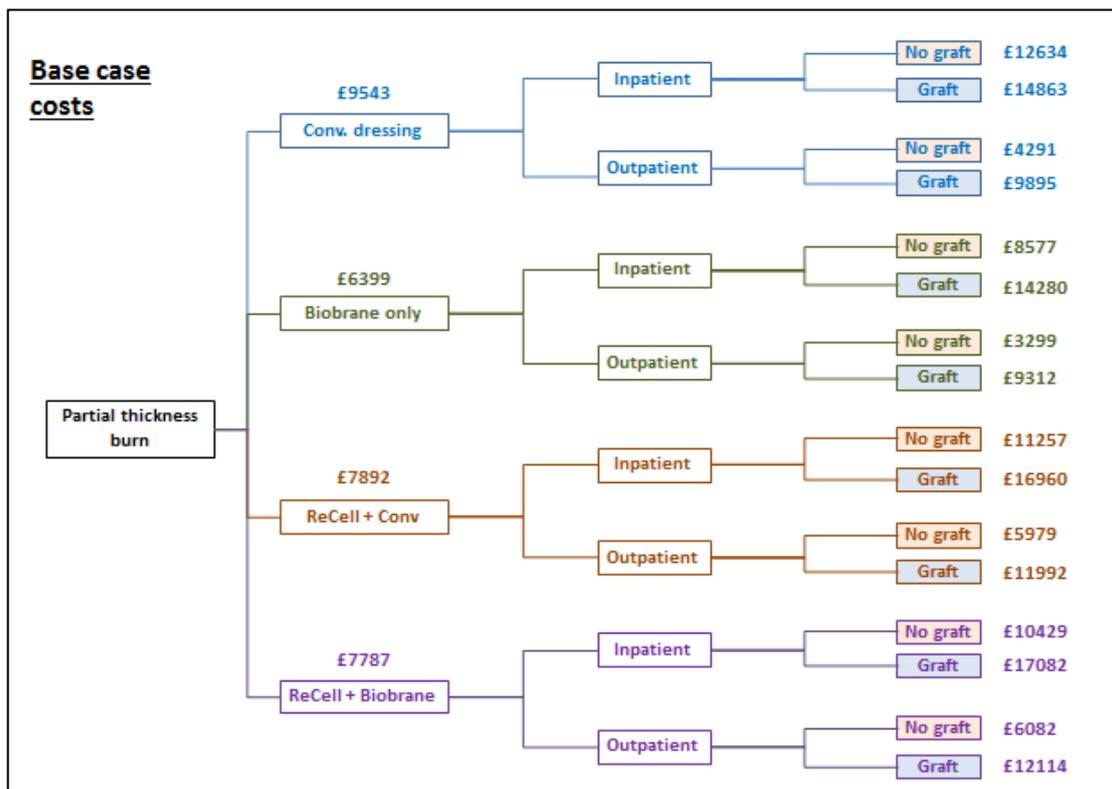


Figure 1 Base case costs used in sponsor’s model (supplied by EAC)

The cost of the ReCell Spray-On Skin system was given by the sponsor and confirmed by the EAC as £950 per 320 cm² (the base-case model was based on 2 packs) and the cost of Biobrane used was £60.80 per 320 cm². Costs for consumables, training and maintenance were not included in the model but the EAC considered this to be reasonable because the device is single use and the manufacturer provides training. The only additional cost the sponsor had included for ReCell was an additional 10 minutes in theatre for debridement and dressing of the initial wound.

Results

The sponsor's base-case analysis showed Biobrane to be the lowest cost treatment (£6398), followed by the ReCell Spray-On Skin system plus Biobrane (£7787), the ReCell Spray-On Skin system (£7892) alone and then conventional dressings (£9543). Biobrane was the lowest cost treatment because of its lower acquisition cost, reduced number of dressing changes and reduced healing time. Cost savings for the ReCell Spray-On Skin system were driven by a reduced proportion of patients needing a standard skin graft and shorter healing times.

The sponsor carried out sensitivity analyses to explore the impact of the uncertainty in various parameters and costs. Results are described for each intervention separately in table C13 on pages 159–62 of the sponsor's submission. The EAC corrected some minor errors in these results (assessment report page 58) with no change in the rank order of cost saving interventions: Biobrane, the ReCell Spray-On Skin system plus Biobrane, the ReCell Spray-On Skin system alone, and conventional dressings.

Table 5 Incremental costs from EAC scenario analysis (negative values indicate a cost saving for the ReCell Spray-On Skin system)

Scenario	ReCell vs conventional dressing	ReCell+Biobrane vs conventional dressing	ReCell vs Biobrane	ReCell+Biobrane vs Biobrane
Base-case (TBSA 640 cm ²)	-£1,651	-£1,756	£1,494	£1,389
TBSA 320 cm ²	£23	£20	£1,146	£1,143
TBSA 1280 cm ²	-£1,148	-£1,680	£3,718	£3,186
Benefits reduced by 50%	-231	-£265	£1,076	£1,042
Hospital costs reduced by 25%	-£1,052	-£1,104	£1,523	£1,471
Hospital costs increased by 25%	-£2,250	-£2,407	£1,463	£1,306
Abbreviations: TBSA total burn surface area				

The sponsor investigated several scenario analyses that included varying the total burn surface area (320 to 1280 cm²) and the in-hospital costs (section 4.3 of the assessment report). The EAC corrected some errors and re-ran these scenario analyses (see table 5) and showed that the ReCell Spray-On Skin system was cost saving compared with conventional dressings except when treating a smaller wound site of 340 cm². In this case both the ReCell Spray-On Skin system and ReCell plus Biobrane were more expensive than conventional dressings. The EAC concluded that the sensitivity and scenario analyses findings demonstrated the robustness of the sponsor's model.

Additional work presented by the EAC

The EAC used NHS reference costs to validate costs used in the model and found that overall results were consistent with the sponsor's model.

For completeness, the EAC compared the model results with those reported in the cost analysis by Wood et al. (2012). This found standard dressings were the lowest cost intervention followed by the ReCell Spray-On Skin system plus Biobrane, and that Biobrane alone was the most costly intervention. The EAC identified as factors that may have contributed to these different results the differences in clinical practice between Australia and UK, differences in patient population and the small number of patients (n=13) in the study.

The EAC could not find any evidence that the ReCell Spray-On Skin system reduced the number of patients who progressed to having a standard skin graft. It therefore expanded the range of the sensitivity analysis from 5–20% to 5–30%. Although this increased the total cost of the ReCell Spray-On Skin (£9079) it still remained cost saving compared with conventional dressings (£9543). The EAC also expanded the range of costs for changing dressings but the results showed the ReCell Spray-On Skin system was still cost saving compared with conventional dressings (see tables 18–21 in the assessment report, p60).

Conclusions about the economic evidence

The EAC considered there were some limitations to the model. The sponsor used data provided by 4 experts to populate the model but the information and description provided to the experts when describing burn type differed from those in the population being considered. The expert opinions differed about the proportion of patients needing standard skin grafts (see table 12 in the assessment report for details). The EAC agreed that 3 of the experts were likely to be familiar with UK practice but they considered that the fourth expert, who had experience working in Australia, was less pertinent. This expert was also one of the ReCell inventors and may therefore have a conflict of interest. The model also relied on unpublished cost data

The EAC concluded that the sponsor's model was robust in the 1-way sensitivity analysis and scenarios modelled except for the treatment of smaller burns (320 cm²: 2.5–5% total burn surface area).

5 Ongoing research

The EAC identified 1 ongoing multicentre randomised, within-patient controlled feasibility study that fitted the decision problem. The trial is being carried out in the USA in collaboration with the Department of Defence in order to gain an FDA licence for the ReCell Spray-On Skin system.

The sponsor also identified a second trial but this was outside the scope because it investigated the use of the ReCell Spray-On Skin system in treating scars from skin grafts.

6 Issues for consideration by the Committee

6.1 *Clinical evidence*

Efficacy of the ReCell Spray-On Skin system for burns that do not need grafting

There was limited clinical evidence in this patient group. The EAC considered that Woods et al. (2012) was the most relevant study. This reported results from a small trial in children who had a scald injury greater than 2% total burn surface area that was expected not to heal within 10 days and therefore likely to benefit from surgery. The results suggested that the ReCell Spray-On Skin system plus Biobrane may reduce healing time and reduce the number of patients who need subsequent grafting compared with both Biobrane alone and standard dressings. The EAC noted there is no evidence comparing the use of the ReCell Spray-On Skin system alone with the use of Biobrane alone.

Efficacy of the ReCell Spray-On Skin system for burns that need grafting

The EAC agreed with the sponsor's conclusion that the ReCell Spray-On Skin system is at least as effective as standard skin grafting in the treatment of partial thickness burns in terms of wound healing and scar outcomes. It disagreed with the sponsor's claim that the ReCell Spray-On Skin system plus standard skin graft demonstrated more rapid healing than a standard skin graft alone. This comparison has been investigated only in the study by Park et al. (2013), which did not report healing rate outcomes. The EAC also

highlighted that the claim that the ReCell Spray-On Skin system plus Biobrane provides more rapid healing, lower costs and shorter length of hospital stay than a standard skin graft is weak because it was based on only 1 study of 15 patients (Rawlins et al. 2011a). The EAC stated that the evidence also suggested that the use of the ReCell Spray-On Skin system is associated with an increase in operative time, and there was no evidence to demonstrate that the ReCell Spray-On Skin system added any additional clinical benefit to Biobrane.

6.2 Additional evidence identified by the External Assessment Centre

The EAC identified 9 additional conference abstracts that were not presented by the sponsor. The EAC reported that 6 of these abstracts presented data from studies that were the same as or overlapped with those presented in the sponsor's evidence. Where possible the EAC contacted authors to confirm the duplication or overlap but they received few responses. Three of the abstracts provided new information, although 2 may have reported the same study. The EAC commented that these additional references did not add substantially to the evidence because of the low levels of detail in the abstracts.

Hypopigmentation

The EAC excluded 2 conference abstracts (Echlin 2012b; Palombo 2012) identified by the sponsor in their main literature search, because the EAC did not consider them relevant to the decision problem. The EAC also excluded all evidence the sponsor collated identifying pigmentation outcomes in people with hypopigmentation (scars and vitiligo) because the patient groups and wound types were outside the decision problem. The EAC confirmed with experts that these outcomes in these populations could not be extrapolated to acute burns patients. Several of the studies reported scar quality outcomes using numerical scales but pigmentation is not reported separately.

6.3 Economic evidence

Limited availability of evidence to support modelling assumptions

The EAC considered that the evidence underpinning the model is very limited and some of it is of questionable suitability, given the heterogeneity of the patient population, the multiple ways of grouping burn injuries and the variable nomenclature used. The EAC recognised that it was a challenge for the sponsor to ensure that all the model inputs were based on the chosen patient population. The evidence was taken from a small number of published and unpublished studies, often with different populations. Expert opinion was used to bridge gaps in the evidence but the advice obtained was varied. The EAC also noted that the model relied quite significantly on an unpublished study for cost data [REDACTED] for which little information about data acquisition and cost derivation is known.

Robustness of the results

Despite the paucity of data, the EAC considered that the sponsor had produced a model for 1 of the population groups specified in the scope: those with partial burns that do not need grafting. The EAC considered the model fit for purpose and was able to validate it using NHS reference costs. Results from the model were shown to be robust in 1-way sensitivity analysis and in scenario analysis conducted by the sponsor and expanded by the EAC, except for a scenario analysis that involved smaller burns (320 cm²: 2.5–5% total burn surface area).

The sponsor considered that the lower costs for Biobrane alone reflect an inappropriate comparison. It noted that Biobrane is mostly used in patients with smaller or more superficial burns, and it considered that it would not be used in isolation for the types of burns for which the ReCell Spray-On Skin system might be considered.

The EAC noted that the important factors in the ReCell Spray-On Skin system being cost saving compared with conventional dressings are the reduction in the proportion of patients needing a standard skin graft and the shorter healing time. The EAC also highlighted there was little evidence for the

parameters used in the model for these clinical outcomes, especially for the ReCell Spray-On Skin system plus conventional dressings intervention, for which there was only 1 small case series study. (Rennekampff et al. 2011).

No cost analysis for large area burns

The sponsor did not provide an economic model for the patient group specified in the scope: 'large area burns; full thickness or deep partial thickness burns including where mesh grafting is required' because of insufficient evidence to provide input parameters. The EAC did not disagree with this. There is some clinical evidence that suggests that the ReCell Spray-On Skin system can be used instead of standard skin grafting for certain burn types and this is likely to have potential cost saving implications.

7 Authors

Caroline Hall, Technical Analyst

Bernice Dillon, Technical Adviser

NICE Medical Technologies Evaluation Programme

November 2013

Appendix A: Sources of evidence considered in the preparation of the overview

A Details of assessment report:

- Peirce S, Carolan-Rees G. The ReCell Spray-On Skin system for treating skin loss, scarring and depigmentation after burn injury, October 2013. Cedar

B Submissions from the following sponsors:

- Avita Medical Ltd (manufacturer)
- JB Medical Ltd (sponsor)

C Related NICE guidance

Published

- [moorLDI2-BI: a laser doppler blood flow imager for burn wound assessment](#). NICE medical technology guidance 2 (2011)

Under development

- Trauma services: service delivery of trauma services, NICE clinical guideline. Publication expected October 2014
- Major trauma: assessment and management of major trauma, NICE clinical guideline. Publication expected June 2015

D References

Dunne J, Rawlins J (2012a) Early Paediatric Scald surgery - developing a (cost effective) dermal preserving surgical protocol for all childhood scalds [abstract]. In: Proceedings of the 16th Congress of the International Society for Burn Injuries, 9th – 13th September 2012, Edinburgh, Scotland. Abstract 716

Dunne J, Rawlins J (2012b) A comparison of ReCell and split thickness skin grafts in management of paediatric burns [abstract]. In: Proceedings of the 16th Congress of the International Society for Burn Injuries, 9th – 13th September 2012, Edinburgh, Scotland. Abstract 718

Rawlins J (2011a) Treatment of deep dermal burns to the legs – a comparative pilot study [abstract]. In: Proceedings of British Burns Association Annual meeting, 22nd-25th March 2011, Salisbury District Hospital, UK.

Rawlins J (2011b) Early surgery for ALL paediatric scalds – developing a dermal preserving protocol for the benefit of patients and healthcare providers [abstract]. In: Proceedings of the American Burns Association 43rd Annual Meeting American Burns Association, 29th March – 1st April, Chicago, Illinois.

Rawlins JM (2013) ReCell versus split-thickness skin grafts in the management of deep dermal paediatric Scalds. In Chinese Burns Association

Rennekampff H, Herold C, Vogt M (2011) Keratinocyte suspension for the treatment of facial burns. European Burns Association. Burns 37 (September): S17

Sen S, Ives M, Philp B et al. (2012) Use of split thickness dermal grafts in combination with sprayed keratinocytes in burns [abstract]. In: Proceedings of the 16th Congress of the International Society for Burn Injuries, 9th – 13th September 2012, Edinburgh, Scotland. Abstract number 693

Sood S, Roggy D, Zieger M (2009) Preliminary results with the use of spray keratinocytes in the treatment of partial thickness burns. European Burns Association Congress. Burns 35 (September): S20

Wood F, Martin L, Lewis D et al. (2012) A prospective randomised clinical pilot study to compare the effectiveness of Biobrane synthetic wound dressing, with or without autologous cell suspension, to the local standard treatment regimen in paediatric scald injuries. Burns 38: 830–9

Appendix B: Comments from professional bodies

Expert advice was sought from experts who have been nominated or ratified by their Specialist Society, Royal College or Professional Body. The advice received is their individual opinion and does not represent the view of the society.

Miss Isabel Jones

Burns Consultant, British Association of Plastic, Reconstructive and Aesthetic Surgeons

Dr Rebecca Martin

Lead Anaesthetist & Intensivist, Association of Burns & Reconstructive Anaesthetists

Dr Sarah Pape

Consultant Plastic Surgeon, British Association of Plastic, Reconstructive and Aesthetic Surgeons and British Burn Association

Mr Bruce Philp

Consultant Plastic Surgeon, British Burn Association

Dr Amber Young

Lead Paediatric Burns Anaesthetist and Paediatric Burns Network Lead Title, Association of Burns & Reconstructive Anaesthetists

- Of the 5 experts who responded, 3 have had direct experience of ReCell, 1 has managed patients in whom it has been used and 1 would like to use the technology. One expert has conducted research on the technology
- Three experts felt that the technology was thoroughly novel, 1 that it was a significant modification of existing technology and 1 that it was a significant modification of an existing technology
- All 5 experts said that the technology would be used to aid wound healing in burns patients, particularly in partial thickness burn injuries; 1 expert also felt it could be used in superficial burns. Two experts were of the opinion that that ReCell would be particularly useful for those with larger or difficult-

to-heal wounds and another felt that this could reduce the need for skin grafting. If ReCell were used in conjunction with skin grafting, 2 experts thought that it could improve the healing time and aesthetic appearance of meshed grafts. One expert considered ReCell would be useful for resurfacing of mid to deep-dermal burns for quicker healing and less scarring, repigmentation of depigmented skin in scars and vitiligo.

- The comparators were stated as split thickness skin grafts, biological dressing, cultured autologous keratinocytes (although the expert did comment these were rarely used and 2 experts explained that ReCell was quite different to cultured autologous keratinocytes) and camouflage make-up.
- No similar competing technologies were identified.
- Four experts were of the opinion that ReCell could aid wound healing, improving speed and quality for burn injuries including large burn areas, meshed grafts, or partial thickness scalds as well as donor sites. Two experts specifically mentioned the potential for ReCell to improve pigmentation in burn injuries and 3, a reduction in scarring. Two experts felt that the improvements in healing could reduce length of stay, and 1 that this could therefore facilitate a faster return to normal activities of daily living. One expert suggested ReCell could improve the appearance of scars.
- The main obstacles to realising the benefits in practice were thought to be cost, with 1 expert also mentioning technical ease of use and another suggesting the use of anaesthesia may be a barrier.
- Four experts thought that the technology would benefit the healthcare system by reducing resource use, such as dressings, analgesia (as a result of a reduction in pain), antibiotics or other therapy, and associated costs. Three experts said that the device could reduce the length of hospital stay. A reduction in scar appearance and improved functionality, as a result of using ReCell, could also reduce the need for future scar management interventions. One expert considered that fewer patients may have long-term psychological distress from scars and skin depigmentation.

- Four experts felt that some training would be needed to use the device, although 2 commented that the technology was easy to learn and use subsequently. One expert suggested appropriate storage would need to be provided.
- Three experts thought that the potential for ReCell to promote faster and better wound healing would reduce overall management costs and would offset the cost of the device. Another expert felt that cost savings would be achieved by the immediate accessibility of the ReCell-prepared suspension when compared against cultured cell suspension techniques. One expert didn't know how the introduction of the technology would affect costs but thought the cost of training and the technology would have to be taken into account.
- All the experts felt that guidance on the device would be useful.

Appendix C: Comments from patient organisations

Advice and information was sought from patient and carer organisations. The following patient and carer organisations responded at briefing note stage:

- The Vitiligo Society

This society and patients were outside the scope of the Decision Problem.

No further societies responded during the evaluation stage.

Appendix D: External Assessment Centre correspondence

National Institute for Health and Care Excellence External Assessment Centre correspondence

The ReCell Spray-On Skin system

The purpose of this table is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the sponsors' original submission. This is normally where the External Assessment Centre:

- a) become aware of additional relevant evidence not submitted by the sponsor
- b) need to check "real world" assumptions with NICE's expert advisers, or
- c) need to ask the sponsor for additional information or data not included in the original submission, or
- d) need to correspond with an organisation or individual outside of NICE

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is made available to MTAC. The table is presented to MTAC in the Assessment Report Overview, and is made available at public consultation.

Submission Document Section/Sub-section number	Question / Request <i>Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.</i>	Response <i>Attach additional documents provided in response as Appendices and reference in relevant cells below.</i>	Action / Impact / Other comments
Section 7.1 Appendix 1	Sponsor (J Belsey) – requested detailed search strategy appendix missing from the Clinical Evidence submission (19/08/13)	Appendix 1 received by email on 20/08/13	
(1-3) Section 7.1 (4) Section 5 (5) Section 4	Sponsor (JB) to request additional information: (1) Manufacturer’s list of studies (2) Search platform used for reference databases (3) Explanation of search terms (4) Ongoing study clarification (5) Declaration of Conformity (22/08/13)	Response received by email on 22/08/13 with requested information attached (Declaration of Conformity and manufacturer’s list of studies). Email response included in Appendix 1.	
Section 7	Author (Gravante) – email requesting additional information regarding the method of randomisation in their study (Gravante et al, 2007), on 23/08/13 and again on 03/09/13	No response.	
Section 7	MTEP clinical expert advisors were asked their opinion regarding the generalisability of the evidence regarding hypopigmentation. (10/09/13).	One advisor responded by email but had misinterpreted the question. The email was resent with clarification. They responded with the opinion that hypopigmentation evidence was not generalisable.	

Submission Document Section/Sub-section number	Question / Request <i>Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.</i>	Response <i>Attach additional documents provided in response as Appendices and reference in relevant cells below.</i>	Action / Impact / Other comments
		Two advisors responded but felt unable to answer the question. One adviser did not respond. Emails attached as Appendix 2.	
Section 7	The sponsor (JB) was contacted regarding how they had obtained the conference proceedings, which were not available on the Web. (13/09/13)	Sponsor (JB) replied stating that manufacturer supplied the conference abstracts and he will forward missing ones to the EAC. Attached as Appendix 3	
Section 9.2.5	Sent email to sponsor (JB) requesting the questionnaire and responses used in the economic evidence. Also email address for J Rawlins. (18/09/13)	JB sent questionnaire and 4 responses, plus J Rawlins email address. Also information regarding ISBI 2012 conference abstracts. Attached as Appendix 4.	
Section 7	Sent email to J Rawlins with questions about conference abstracts. (19/09/13). Reminder sent on 25/09/13).	Response on 27/09/13 stating that all publications without F Wood's name on	

Submission Document Section/Sub-section number	Question / Request <i>Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.</i>	Response <i>Attach additional documents provided in response as Appendices and reference in relevant cells below.</i>	Action / Impact / Other comments
		were conducted in Wakefield, UK. Attached as Appendix 5.	
Section 5.1	Sent email to JB requesting clarification on the ongoing trials. (20/09/13)	Received email clarifying the trial identifiers. (20/09/13). Attached as Appendix 6.	
Section 7	Sent email to J Dunne regarding conference presentations. (25/09/13)	Got response on 26/09/13 asking J Rawlins to be included. Returned email with specific questions. Got response on 30/09/13 indicating study overlap & locations. Attached in Appendix 7.	
[REDACTED]	[REDACTED]	[REDACTED]	
Section 3 Section 9	Sent email to expert advisers requesting information about clinical pathway (27/09/13)	Got email response from 1 adviser and telephone conversation (followed up with email) with another adviser. Attached in Appendix 9	

Submission Document Section/Sub-section number	Question / Request <i>Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.</i>	Response <i>Attach additional documents provided in response as Appendices and reference in relevant cells below.</i>	Action / Impact / Other comments
Section 7	Sent email to B Philp regarding overlap between Sen et al. (2012) and Philp et al. (2013). (30/09/13)	Received information that Sen et al. (2012) was a feasibility study for Philp et al. (2013). Attached in Appendix 10	
	Sent email to expert advisers regarding the use of meshing in skin grafts. (07/10/13)	Got response from three advisers indicating that meshing is quite common Attached in Appendix 11	
Section 7.7.2 - 7.7.4	Sent email to expert advisers regarding advice to patients regarding trypsin and sodium lactate. (09/10/13)	Got response from three advisers indicating routine advice to patients about trypsin and safety of lactate. Attached as Appendix 12.	
	Sent email to expert advisers regarding the use of ReCell in combination with SSG. (10/10/13)	Two advisers indicate that ReCell would be used with higher mesh grafting in larger burns. Attached as Appendix 13.	
2.1	Sent email to sponsor to clarify the use of the word 'thinness' when describing meshed grafts. (16/09/13)	Advised that 'thinness' related to the thickness of	

Submission Document Section/Sub-section number	Question / Request <i>Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.</i>	Response <i>Attach additional documents provided in response as Appendices and reference in relevant cells below.</i>	Action / Impact / Other comments
		the graft and not the mesh ratio. Report wording amended as per Sponsor's Fact Check. Attached as Appendix 14.	

Appendix 1

From: Susan Peirce
Sent: 22 August 2013 11:12
Hi Jonathon

Nice to speak with you this morning. Here are my initial queries, mainly regarding the search strategy:

1. Please send us the list of studies that were in the 'Manufacturer's database of known studies'.
2. What platform did you use to access the literature databases? We use OVID and NEAR is not an operator defined on this platform (we use 'adjacent' with a number to stipulate how many words distance). Please can you let us know how NEAR is defined?
3. What was the rationale for using the search phrase 'autologous NEAR cell NEAR harvest*'? Did you have any information from the manufacturer that this was the preferred alternative if authors didn't use the brand name?
4. Please can you confirm the national clinical trials identifier for the study identified in the Ongoing Studies section (5.1, p21). This has similarities to NCT01476826 (<http://clinicaltrials.gov/ct2/show/NCT01476826>). Also, do you have additional information regarding study NCT01138917 (<http://clinicaltrials.gov/ct2/show/NCT01138917>), intended to complete in March

2014? Maybe the manufacturer has more up-to-date information that this study information will not be available within 12 months.

5. Please send us a Declaration of Conformity for the CE mark? We have three certificates for the manufacturer's quality systems, but there should also be a certificate declaring ReCell's conformity with the Medical Devices Directive and stating its classification.

I'll be in the office until about 3:15pm today. I can phone you or you can call me direct on the number below.

Sue Peirce (Dr)
Research Associate
School of Engineering
Cardiff University

Hi Sue

1. I have attached the list of studies provided by the manufacturer
2. I carried out my searches using the search engine on the Royal Society of Medicine members system. The platform that they use is ProQuest Dialog. The NEAR function is the same as the ADJACENT function in Ovid – in this case I used the default setting of within 3 words, although it can be specified otherwise
3. The manufacturers advised me that the description of the technology is “non-cultured autologous cell harvesting”, although the full term would not necessarily be used as it stands in an article. Because we applied an exclusion of cultured cell harvesting studies after the search, I used only the last three words of the term. In order to capture all possible instances of this (eg a statement in the abstract that “an autologous cell sample was harvested from near the wound site” I adopted the NEAR function and based it on text words. In the event, no study was identified purely on this basis.
4. Yes, the ongoing study mentioned is NCT01138917, which has now finished recruiting although not all patients have yet completed 6 months follow-up. Study NCT01138917 is being carried out to provide data for a US FDA submission. As I understand it there have been issues with slow recruitment so that the time frame has been extended and it is now not expected to report until 2015 at the earliest and is hence outside the twelve month window.
5. Declaration of conformity attached

I will ring you to confirm that these answer your queries
Kind regards

Jonathan

Appendix 2

From: Susan Peirce (Cardiff and Vale UHB - Cedar)

Sent: 10 September 2013 16:26

Hello

I'm writing to ask your expert advice with regards to the current NICE evaluation of ReCell for burn injury. The Scope defines this as an evaluation of the evidence for ReCell in partial to full thickness burns in comparison to standard care (dressings or grafts, as appropriate).

Particular mention was made in the Scope about the effect of ReCell treatment on pigmentation of the burn scar, especially with reference to patients with darker skin. To address this the sponsor has included studies that evaluate ReCell for the treatment of hypopigmentation; the indications are essentially scar revision and vitiligo. My initial reaction is that data relating to repigmentation of these lesions following treatment with ReCell would not be generalisable to pigmentation outcome from treatment of an acute burn wound with ReCell. However, I'd like your clinical opinion as to the similarity between these indications (acute burns versus hypopigmentation), i.e. how transferable are outcomes reported in hypopigmentation patients to outcomes expected in patients with burns?

Thank you.

Sue

Sue Peirce (Dr)

Dear Sue

Thank you for the conversation. I hope it helped. I have a few changes to the content below as regards our conversation. Please do get back in touch again if I can help.

Best wishes
Amber

- Your expertise is the in treatment of acute burns and the affects of acute treatements on outcomes including scar formation. You have no clinical experience of repigmentation treatments for burn scars or vitiligo.
- You are not an expert in the long-term outcomes for burns relating to de-pigmentation
- Although scar quality is an important outcome for burns treatment there is little mention of comparative methods of treating burns acutely and the effect this has on pigmentation of burn scars at clinical conferences or research journals.
- You suspect that outcomes from using ReCell in repigmentation treatments for non-burn cases cannot be extrapolated to its use in burns.
- It may be worth asking the other clinical advisors if they have any data/information regarding pigmentation outcomes in burns managed using different strategies including ReCell.

Dr AER Young
Consultant Paediatric Anaesthetist, Lead Specialist Paediatrics

Sue

Thank you for the email and sorry for delayed response.

This is not really an area of expertise for me as I feel my surgical colleagues would be best placed to answer on this point.

I work with Bruce Philp, who I think you emailed, and believe his response would be more valid then mine.

From what I have witnessed in clinical practice I would agree with Isabel Jones's statement.

Sorry not to be more helpful on this point, please let mw know if there is any other way in which I can help.

Kind regards

Rebecca

Dr Rebecca Martin
Consultant in Burns Anaesthesia and Intensive Care & College Tutor

Yes, happy with this thank you.

Isabel Jones MBBS MD FRCS(Plas)
Consultant Burns and Plastic Surgery

From: Susan Peirce
Sent: 23 September 2013 09:52
Isabel

Thank you for calling this morning. I've summarised the content of our conversation – please alter anything that I've misrepresented/misunderstood or add anything that you have thought of in the meantime. This email will be included in our report to NICE.

- In your experience treatment of burn wounds with ReCell (including in patients with darker skin) appears to produce better skin pigmentation than would have otherwise been expected, but this is anecdotal and there is no published evidence to support this.
- Pigmentation outcomes following the treatment of old scars and vitiligo with ReCell cannot be extrapolated to treatment of acute burns. An acute burn wound is more complex than a surgical wound created by debridement of scars or vitiligo lesions.

Thank you,

Sue

Appendix 3

Hello Sue

Sorry about the NEAR issue - thankfully the economics search doesn't use any of these terms, so it should be simpler.

I got hold of the conference listings (and the abstracts) from the manufacturer - they tend to be at all the meetings and collect them. There is a great deal of duplication involved here, with the same work being presented at several conferences - often with different authors listed just to confuse things further.

I am out of the country now until Wednesday morning now, with only limited access to my files. I will have a look through your list and see if I have any of these with me. If not, I will sort it out when I return next week. Hope this is OK

Kind regards
Jonathan

On Fri, Sep 13, 2013 at 3:11 PM, Susan Peirce wrote:
Hello Jonathon

Regarding the clinical evidence, I've attempted to replicate your search strategy using Ovid and retrieved 32 records. I don't think we need to worry about the extra 2 records – I found that using the operator 'AJD3' (Ovid) didn't produce the same results as the operator 'NEAR' (ProQuest Dialog) so in the end I just used 'AND'.

I've reviewed the literature search you conducted and have a question.

How were you able to access the conference proceedings? I've located all three of the EBA conferences, two each of the BBA and one of the ISBI (either online or hardcopies that I already had). In particular Avita press releases indicate eight relevant presentations at the 2012 IBSI/BBA meeting in Edinburgh, of which five are included in your clinical evidence submission. However,

the website for this conference has expired. Did you manage to obtain the proceedings from the organisations? If you have electronic copies of the programmes/abstracts please could you forward them to me? I've attached a summary of additional references that I've located and the conferences I've checked so far.

This was rather confusing due to the number of similar references – I suspect a lot of overlap.

Sue Peirce (Dr)
Research Associate

Appendix 4

Hi Sue

1. I have attached the questionnaire and responses
2. Jeremy Rawlins e-mail address is: [*text removed*]
3. Regarding last weeks request – I will forward the ISBI 2012 abstract file to you. Unfortunately it is very large (100Mb+) so I will have to send it on a disk. At the moment I can only track down a hard copy version of the BBA 2013 abstracts. I am trying to find it electronically, to avoid a lot of photocopying. As it happens, there were no ReCell abstracts at this meeting.
4. I have also tracked down the issue that explains why sections A+B were different between the original and subsequent submissions – the manufacturer had inserted some new references into the file between my finishing it and it being submitted. I have now forwarded the correct file to Caroline, which she will presumably forward on to you. Unfortunately this has changed the reference numbering, so I will also forward to you a new disk with the revised numbering. Sorry for the mix-up.

Kind regards

Jonathan

Appendix 5

From: Jeremy Rawlins
Sent: 27 September 2013 15:17

Sorry, have been overwhelmed with rather a busy stint of on-call and then interstate travel (and catching-up with emails). Will follow-up on this as I can, but to answer your question on studies - all of my stuff without Fiona Woods' name on have come from my UK Cons practice in Wakefield. Hope this is helpful.

J

Appendix 6

From: Jonathan Belsey
Sent: 20 September 2013 12:20

Hi Sue

Sorry – typo in the first sentence of my reply. I should have said:

4. Yes, the ongoing study mentioned is NCT01476826, which has now finished recruiting although not all patients have yet completed 6 months follow-up. Study NCT01138917 is being carried out to provide data for a US FDA submission. As I understand it there have been issues with slow recruitment so that the time frame has been extended and it is now not expected to report until 2015 at the earliest and is hence outside the twelve month window.

Kind regards

Jonathan

From: Susan Peirce
Sent: 20 September 2013 12:04

Hi Jonathon

I've just gone back to this email in writing up my report and I've noticed that the answer to Q4 is a bit confused. Did you mean to say that the ongoing study mentioned is NCT01476826?

Sue

Appendix 7

From: Jonathan Dunne
Sent: 30 September 2013 19:21
Dear Sue,

Study 4 was conducted at Pinderfields and Royal Perth Hospital, Australia. It will be my affiliation that you may have seen as different elsewhere, but all procedures have been undertaken by Mr Rawlins at Pinderfields or Royal Perth. Abstract 4 is a retrospective review of Mr Rawlins' cases, and an update on previous presentations so there is some overlap with abstracts 1 and 3, and a small amount of overlap with 2, although that did include predominantly non-recell patients. Abstracts 3 and 4 had patients in with adequate follow-up photographs, and as they were retrospective studies there was some loss to follow-up. Abstract 1 includes patients with different follow-up timings and therefore scar assessments, which is where the differences arise from.

I haven't been through the patient data that Mr Rawlins has produced with other authors, but I believe there will be a degree of overlap with reference 4.

Hope this helps.
Kind regards,
Jonathan

On Fri, Sep 27, 2013 at 11:02 AM, Susan Peirce wrote:

>
> Thanks Jonathan
>
> I have emailed Jeremy Rawlins, but I've had no response and am on a short timescale.
> The references that I thought you might be able to help me with are:
>
> Rawlins (2013):

- > (1) ReCell versus Split-Thickness Skin grafts in the Management of Deep Dermal Paediatric Scalds. Chinese Burns Association
- >
- > Dunne & Rawlins (2012)
- > (2) “Early Paediatric Scald surgery – Developing a (cost effective) dermal preserving surgical protocol for all childhood scalds.” – ISBI, Edinburgh
- > (3) “A comparison of ReCell and split thickness skin grafts in management of paediatric burns” - ISBI, Edinburgh
- >
- > Dunne & Rawlins (2013)
- > (4) “How we do it. Early dermal salvage with Biobrane and ReCell in the management of Deep Dermal Burn Wounds” - European Burn Association, Vienna
- >
- > I have copies of the abstracts.
- >
- > 1. (3) and (1) appear to be the same patient population, but with an extra 5 patients in the 2013 presentation. Was this study retrospective? Was it conducted at Pinderfields? There appears to be a marked difference in the scar assessments that isn't explained by the additional patients – do you know why this is?
- >
- > 2. Where was (4) conducted? Are the 11 paediatric scald patients the same as those included in (3) and (1)?
- >
- > 3. Can you confirm that (3) was conducted at Pinderfields? Is there some overlap with the other studies.
- > I also have 3 references for Jeremy Rawlins (solo & in combination with 3 other authors) on a series of deep flame burns (mostly legs) – I thought these were conducted in Australia, but it's unclear. I just wondered whether these patients might also be include in reference (4).
- >
- > I know that both you and Jeremy have moved about a bit and when presenting it's most likely that the affiliation at the top is your current one rather than the place where the study took place. If you have any other information about these studies that you can provide (e.g. the slides) I would also be grateful for that.
- > Sue

Appendix 8

From: Jonathan Belsey
Sent: 26 September 2013 14:27

Sorry – missed your second question. From what I understand, they carried out a prospective audit of resource utilisation, documenting all elements of care for 22 successive patients. They then sourced unit costs for each element from the Trust administration and applied these to the documented resources.

J

Appendix 9

From: Jones, Isabel
Sent: 01 October 2013 13:44

Response in blue below. (Italic & underlined for clarity – EAC)
 I will be away on leave from the 3rd-6th October.
 Kind regards

Isabel Jones MBBS MD FRCS(Plas)
 Consultant Burns and Plastic Surgery

From: Susan Peirce
Sent: 27 September 2013 18:16

Hello Isabel

I have some more questions. Please also correct any incorrect assumptions below.

This is the way the patient population/intervention/comparator combinations are split in the scope for this evaluation:

	Population	Intervention	Comparator
Group A	Partial thickness burns including scalds caused by hot water where mesh grafting is not required	ReCell alone, or in combination with biosynthetic or standard dressings	Biosynthetic dressings OR standard dressings
Group B	Large area burns; full thickness or deep partial thickness burns including where mesh grafting is required	Skin mesh graft in combination with ReCell	Skin mesh graft alone OR skin mesh graft plus biosynthetic dressing

1. For burns that are dressed with conventional (not biosynthetic) dressings – where does this happen Usually on the ward, unless too large to tolerate pain, between 5 & 10% TBSA. Do these patients need to remain as inpatients *because* dressing changes are done in theatre No, only if they cannot manage at home because of size/ site of burn or pain? How many and what grade of staff are needed for this? How long would it take? Does this depend on TBSA? Theatre change of dressing (COD) are done by doctors, ward COD by nurses. Theatre staff is 6+, ward is 1-2 nurses. Time to do dressing change depends on size of burn, site of burn and psychology of patient
2. For burns that are treated with ReCell and covered with conventional dressings I understand that ReCell should not be disturbed for 5 days. Do the secondary dressings on top get changed in this time? Are the dressing changes after this conducted in the same way as for question 1? We change the secondary dressing at 48 hours to check for infection, then every 3– 4 days. Subsequent dressings are generally far quicker and more pain free than with conventional dressings. See note below*
3. For burns that are treated with Biobrane (with or without ReCell) I understand that the Biobrane is left undisturbed (unless infection etc. occurs) until it lifts of its own accord, but that it would have a secondary dressing on top. Where & how would this dressing be changed, and by whom? The secondary dressing is changed by a nurse, generally in OP after the first review.
4. Would you use ReCell on partial thickness burns that you expect to heal without surgery, i.e. burns that you would dress with conventional or biosynthetic dressings (Group A)? We haven't identified any studies in this group. Yes. Jeremy Rawlins and Fiona Wood have presented this work internationally, predominantly in paediatric scalds.
5. How widely used is Biobrane? Is this standard care for certain burn injuries? Yes
6. Do you use the MoorLDI burns imager? Is this widely used to assess burn depth? Yes
7. Most of the published evidence available compares ReCell (alone or with Biobrane) to SSG in partial thickness burns, but this doesn't fit the groups defined above. It appears that ReCell (without graft) is being used in mid-deep dermal burns as an alternative to SSG and that ReCell plus SSG would only be used in deep/full thickness burns. Does this seem correct to you? Would this be a more appropriate division of the population/treatment groups? Yes
8. The sponsor indicates that partial thickness/indeterminate burns would be dressed and then reassessed about a week later. Several of the clinical studies examine the use of 'early' surgical intervention, i.e. treating with ReCell, Biobrane or SSG at around day 2-3 post injury. Please could you indicate what the standard practice is at your centre? Can you estimate how widely used each protocol (early intervention versus wait-and-see) is in the UK? Both are standard, depending on the scenario, but the earlier approach more often the case: The gold standard is to excise and definitively treat the burn on the next available routine list (24-72 hours usually, aiming for day 1 rather than day 2-3). Unfortunately the laser Doppler is most accurate 2-5 days post burn, so in some cases the intervention may be indicated by the laser Doppler several days after the burn, and

Recell may be used later. Occasionally a burn that was expected to come through by 2 weeks is seen to be struggling at 2 weeks and application of Recell at this time may successfully heal it within 3 weeks. Rarely a partial thickness would develop into a chronic wound over a number of weeks (eg a donor site in the elderly population) and use of Recell in these chronic wounds appears to kick start the wound to heal.

Thank you. The deadline for this assessment report is Friday 11th October and I will have more questions for you before then as we try to model the care pathway for the economic assessment. Your input is vital to the assessment in order to make sure the evaluation and model reflect current UK practice.

*If the same size burn can be initially treated in either conventional dressings or biosynthetic (Biobrane/suprathel), the subsequent dressings are more likely to be done with simple analgesia on the ward rather than in theatre. The larger the size of the burn (approaching or > 10%) the more likely the conventional dressings would go to theatre for COD. By definition these are burns that should be healed within 21 days, so we are looking at a maximum of 7 dressings if changed every 3 days.

Sue

Sue Peirce (Dr)
Research Associate
School of Engineering
Cardiff University

From: Young Amber
Sent: 03 October 2013 16:34

Hi Sue
Comments are as per the below.
Please email if you need more info.
best wishes and thanks

Amber

Dr AER Young
Consultant Paediatric Anaesthetist, Lead Specialist Paediatrics

From: Susan Peirce
Sent: 30 September 2013 11:54
Amber

Thanks very much for talking through your answers with me. Here is a summary of your information – please correct or augment this as appropriate. I've added a couple of clarification questions in a different colour

- (1) Conventional dressings: In a specialist burns service adult inpatients would be dressed on a ward and outpatients would be changed in dressing clinics by nurses, paediatric patients (especially with larger burns, >10%) would be dressed in theatre and would therefore require a burns surgeon (not necessarily a consultant). These are painful procedures. A surgeon would review the wound at each dressing change. The time to complete the changes would depend on the burn size, age of the patient, complexity of the wound (e.g. difficult location) and healing stage (new grafts would take longer as more care is needed). Large burns could take a couple of hours to change, smaller burns around 30 mins. Yes.
- (2) Secondary dressings for ReCell: Not sure of answer. Generally conventional primary dressing are not transparent so the wound can't be inspected until this is removed. They are generally changed every 48 hrs. If Recell requires no disturbance for 5 days then I am unsure what 'conventional dressing would be used?
- (3) Biobrane secondary dressings: Biobrane sticks to the wound; it lifts as healing occurs and is trimmed at dressing changes. Changing the secondary dressing (probably dry gauze and bandage) is simple and quick. The wound would be reviewed by a surgeon at the first change (~48hrs) but later dressing changes only require nurses (unless there is a problem – Biobrane is lifting prematurely, wound is pustulant or the patient is ill). Yes

- (4) Burns expected to heal: There is no published evidence for use of ReCell in this group of patients (Group A) that I know of. ReCell is not currently used in these wounds esp if small in area; such burns would be dressed with a biosynthetic dressing if > 2-5% TBSA.
- (5) Biobrane is widely used in the UK, depending on the size of burn. On wounds that are expected to heal, for areas >5% it would be used commonly. For >5% partial thickness scalds (and some burns) that you hope would heal without surgery it improves the speed of healing. (Is there a difference between treating scalds and treating burns?). Yes - scalds are generally treated conservatively (ie without debridement with an attempt to get healing in less than 2-3 weeks without scarring unless very large area or deep PT or FT).
- (6) moorLDI: This is used relatively commonly – it assesses the expected time to heal (not burn depth) and is used at 48 hrs post-injury. Yes
- (7) Division of burn groups: It is very difficult to be clear about this. The extremes of the patient groups are more straightforward; superficial burns (no graft) and deep partial or full thickness burns (definitely graft). Using grafts in the mid-dermal group is controversial. ReCell plus graft may be used, especially on larger burns. Yes
- (8) Early intervention: There is controversy about the management of partial thickness burns (as (7)), especially the smaller ones. In wounds where there is uncertainty about their potential to heal early grafting would not be used unless the burn is very large or the patient very unwell. Generally the burn would be dressed (with standard dressings or biosynthetic esp if > 2-5% TBSA?) and inspected at 2 and 3 weeks to assess likelihood of healing or earlier if patient unwell. Some surgeons would be more aggressive with early intervention, but would use Biobrane not grafts at this stage.

Additional question: Can you define a size range in which ReCell would or would not be used?

<10% - Largest patient group, wide variation in practice, little evidence, ReCell unlikely to be used.

10-20% - Difficult patient group, more likely to use ReCell and grafts.

>20% - Major burn, complex patients, long hospital stay, will use grafts with or without ReCell.

>40% - High risk of death, use everything possible to help patient survive, cosmetic considerations are less important, use grafts and maybe ReCell. Yes

Sue

Appendix 10

From: Philp Bruce
Sent: 30 September 2013 16:11

Dear Susan

the first paper was on the first 5 patients and was presented as a paper at ISBI/BBA 2012. It was indeed a feasibility study. We are putting together an ethics application to do a proper prospective trial.

The second paper is the first 10 patients but has not yet been presented.

best wishes
Bruce

From: Susan Peirce
Sent: 30 September 2013 13:22

Apologies Bruce, I meant to include this question last Friday. This is a question about presentations that you are an author on. Please could you let me know if there is any overlap of patients between these two conference papers. Was Sen et al. a feasibility study or maybe just the first few patients? Thanks

Sen, S., Ives, M., Philp, B., Dziewulski, P., Herndon, D., & Wood, F. 2012, Use of Split thickness dermal grafts in combination with sprayed keratinocytes in burns. In International Society for Burns Injuries Meeting, Edinburgh, Scotland.

Philp, B., Dziewulski, P., El-Muttardi, N., Shelley, O., Mazurek, M., Barnes, D., Ives, M., Sen, S., Lloyd-Hughes, A., Myers, S., Herndon, D., & Wood, F. Dermal grafts combined with ReCell - preliminary clinical results. (Abstract submitted for presentation).

Sue

Appendix 11

From: Young Amber
Sent: 07 October 2013 17:36

Hi Sue.

In general that is right re meshing. You would do a non-meshed graft on 'special' areas. SSGs will be more widely meshed for larger area burns when you have less skin available ie you trade a poorer cosmetic result for a larger area of cover. Re specific numbers and ratios for meshing, you will need to contact one of the surgeons I think. I am not sure that there is a 'rule' though.

best wishes and hope that is OK
Amber

Dr AER Young
Consultant Paediatric Anaesthetist, Lead Specialist Paediatrics

From: Susan Peirce
Sent: 07 October 2013 14:20

Hello Amber

Just a quick question. When split thickness skin grafting is used to treat burns, is it always meshed (except maybe for areas such as hands, face and groin)? Can you provide a rough estimate of what the ratios would be for different size burns?
Thanks

Sue Peirce (Dr)
Research Associate

From: Jones, Isabel
Sent: 09 October 2013 12:06

Hi Sue

I would tend to consider sheet grafts in burns <10% particularly in children and special sites such as the hands and face. 10% is very much the upper limit, with up to 5% being grafted with a sheet graft more usual in reality. However the majority of patients with any size of burn will have a meshed graft (1:1 – 2:1) as generally these take better (but long term look worse...)

The patients are only advised the trypsin is porcine derived if we suspect they will object to this on religious grounds. I have not yet met with an objection & suspect this will happen but only infrequently.

I can't think of a feasible way to test for sensitivity, certainly not in the urgent cases.

The trypsin is rinsed off, as prolonged contact affects keratinocytes viability deleteriously, so there should be minimal if any in contact with the patient.

Sodium lactate is a physiological solution, I am not aware of any reports of sensitivity to this, but have not done a literature search specifically to check.

Hope this helps

Isabel

Isabel Jones MBBS MD FRCS(Plas)
Consultant Burns and Plastic Surgery

From: Susan Peirce
Sent: 09 October 2013 10:14

Thanks for that Isabel,

So, 'smaller burns' would be below about 10%? You would tend to use sheet grafts on this sort of size?

(This is important because of the way that the patient populations have been defined in the scope for this assessment).

Also are patients (or their family) routinely advised about the use of porcine-derived trypsin in ReCell before use? Would there be some way to test for sensitivity to trypsin or sodium lactate before use (this is in the contraindications for the device)?

Sue

From: Jones, Isabel
Sent: 07 October 2013 20:14

Dear Sue

Unfortunately there is not a simple answer!

We use sheet skin on smaller burns for improved cosmesis & potentially function, as in the cases you refer to. In addition it is always a consideration for use in burns up to 10-20% TBSA, when improved aesthetics and pliability have to be weighed up against the larger donor site and potential increases risk of graft loss from seroma under the graft.

The mesh size used varies from surgeon to surgeon and patient to patient, rather than being prescriptive. There are many factors that influence a surgeon's decision, for instance with the elderly with much thinner skin and poor donor site healing, I generally use a wider mesh on a smaller burn to minimise donor morbidity. There is a lot of variability in the use of 1:1 mesh - 3:1 mesh. As a rule in our service once the burn is >40% it is common to use the wider mesh, eg 4:1, and at >55-60% TBSA we use meek micromeshing at 9:1

Regards
Isabel

From: Martin Rebecca
Sent: 09 October 2013 11:00

Dear Sue

Yes -the graft is nearly always meshed with the exception of sheet grafts which are usually reserved for special areas eg hand/ face but occasionally are used elsewhere.

Mesh can be micro/ mini or 1: 1 up to 1:4 , with the larger meshes reserved for the major burns where there are a shortage of donor sites.

There is not a clear and fast rule but the smaller injuries will have less meshing but depends on site of body, whether infected injury and if primary graft procedure or redo following failed graft.

Larger mesh grafts are more fragile and take longer to heal so are usually used with additional allograft to protect them and stop the underlying tissue drying out. They tend to be reserved for when large surface areas of the body need covering.

Kind regards

Becky

Dr Rebecca Martin
Consultant in Burns Anaesthesia and Intensive Care

Appendix 12

From: Martin Rebecca
Sent: 09 October 2013 11:09

Hi

No testing that I am aware of - I expect just an allergy question as per normal.
We use sodium lactate solutions a lot in anaesthesia too.

Our practice would usually be to inform patients if porcine derived products of any nature are used as part of consent process.

Thanks

Becky

Dr Rebecca Martin
Consultant in Burns Anaesthesia and Intensive Care

From: Susan Peirce
Sent: 09 October 2013 11:06

Thanks for that Becky.

Also are patients (or their family) routinely advised about the use of porcine-derived trypsin in ReCell before use? Would there be some way to test for sensitivity to trypsin or sodium lactate before use (this is in the contraindications for the device)?

Sue

From: Jones, Isabel
Sent: 09 October 2013 12:06

Hi Sue

I would tend to consider sheet grafts in burns <10% particularly in children and special sites such as the hands and face. 10% is very much the upper limit, with up to 5% being grafted with a sheet graft more usual in reality. However the majority of patients with any size of burn will have a meshed graft (1:1 – 2:1) as generally these take better (but long term look worse...)

The patients are only advised the trypsin is porcine derived if we suspect they will object to this on religious grounds. I have not yet met with an objection & suspect this will happen but only infrequently.

I can't think of a feasible way to test for sensitivity, certainly not in the urgent cases.

The trypsin is rinsed off, as prolonged contact affects keratinocytes viability deleteriously, so there should be minimal if any in contact with the patient.

Sodium lactate is a physiological solution, I am not aware of any reports of sensitivity to this, but have not done a literature search specifically to check.

Hope this helps

Isabel

Isabel Jones MBBS MD FRCS(Plas)
Consultant Burns and Plastic Surgery

From: Young Amber
Sent: 09 October 2013 10:54

Thanks Sue. Patients should and would routinely be told about porcine-related products of all types during the formal consent procedure. This would be very important for certain religious groups.

Sodium lactate is commonly used in fluids and I have never heard of sensitivity to it. We all have lactate in our blood. I would imagine there is a way to test for sensitivity to both but that would complicate the use of ReCell hugely. I have never heard of this being done.

Best wishes
Amber

Appendix 13

From: Young Amber
Sent: 10 October 2013 12:21

Thanks Sue

I think there is no formal agreement on this as far as I understand.

My understanding is that if the graft needs to be meshed with a high ratio ie the holes in the graft are larger than normal (to be clear!) which would occur when there is a large area of skin loss to cover with little skin available then ReCell would be considered to improve both healing (main aim) and possibly cosmesis. Is that OK?

Best wishes
Amber

On 10 Oct 2013, at 12:14, Susan Peirce wrote:
Hello Amber

We have very little information regarding the use of ReCell with skin grafts. Can you summarise when and why you would use ReCell in addition to skin grafting (meshed or sheet)?

Thank you. (The report is nearly finished, just trying to fill in the last few holes.)

Sue

Sue Peirce (Dr)

Research Associate

From: Jones, Isabel

Sent: 10 October 2013 17:29

There is no indication to use Recell in conjunction with a sheet graft (only if it is being used on the donor, ie indicated for the donor site healing not used in conjunction with the sheet graft).

It is currently used with meshed grafts of $\geq 4:1$ to reduce time to healing

Isabel Jones MBBS MD FRCS(Plas)
Consultant Burns and Plastic Surgery

Appendix 14

From: Susan Peirce (Cardiff and Vale UHB - Cedar)
Sent: 16 October 2013 13:30

Hi Jonathan

Thanks for getting back to me quickly. Just to ensure that we have a written record of our telephone conversation, you stated that the section in the sponsor's submission did refer to the thinness/thickness of the skin graft and not the proportion of meshing. This was to reflect the sponsor's claim that thinner and more widely meshed grafts are at higher risk of graft loss and that the use of ReCell with either of these can reduce this risk.

I will reword that part of the Assessment Report accordingly.

Sue

From: Jonathan Belsey
Sent: 16 October 2013 12:21

Hi Sue

I will be free for a call after about 12.30 – would that be OK for you?

J

From: Susan Peirce
Sent: 16 October 2013 11:56
Hi Jonathan

There have been a couple of additional factual corrections to our report suggested by Avita. (I don't know whether you have had a copy so I've attached one.)

Can you provide some very quick clarification regarding their Issue 1 please? In section 3.5 of the sponsor's submission, 3rd paragraph (starting "ReCell can..."). The penultimate sentence states:

"By using ReCell to spray harvested autologous epithelial cells over the mesh network at the time of application, a thinner graft may be taken without incurring the usual additional risk of graft failure."

This is the first time that the use of thinner skin grafts has been mentioned – the previous text in that paragraph is about meshing of skin grafts. Also the use of a thinner graft is suggested to increase the risk of graft loss, as is a wider meshed graft. I therefore took 'thinner' to indicate a more widely meshed graft. Please can you clarify whether this is what you meant or whether this was actually about the thickness of meshed skin grafts.

Thanks. I have a teleconference with NICE this afternoon and must respond to these points by tomorrow, so I would be very grateful for a rapid response from you. A telephone call may be more appropriate – I could call you if you're available.

Sue Peirce (Dr)
Research Associate
School of Engineering
Cardiff University

Appendix E: Sponsor’s factual check of the assessment report and the External Assessment Centre’s responses

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
<p>On page 9 in the second paragraph under the heading ‘ReCell in the clinical pathway’ the EAC states: “<i>The EAC therefore considers that by ‘thinner’ the sponsor means ‘widely meshed’.</i>” This is a misunderstanding of the terminology.</p>	<p>We would suggest deleting the two sentences starting from “<i>The EAC therefore considers...</i>”</p>	<p>Grafts can either have a narrow or wide mesh, or alternatively a thinner or thicker depth of skin can be used. In either situation, the wider mesh and thinner graft has an increased risk of graft loss, which the use of ReCell diminishes</p>	<p>The EAC thanks the sponsor for their clarification (see EAC’s correspondence table). The paragraph has been altered as follows:</p> <p>From: “<i>The sponsor states that the addition of ReCell to a meshed graft enables thinner grafts to be used. No other reference is made to the thickness of the skin graft elsewhere in the submission. Also</i></p>

			<p><i>the sponsor states that widely meshed grafts have increased risk of graft loss and that ‘thinner’ grafts have an additional risk of graft loss. The EAC therefore considers that by ‘thinner’ the sponsor means ‘widely meshed’. In this way they suggest that the additional application of ReCell to a widely meshed graft will reduce the persistence of the mesh pattern in the healed skin, reduce the risk of graft failure and therefore allow wider meshing to be used more routinely which will reduce the donor site areas required.”</i></p> <p>To: <i>“The sponsor states that the use of thinner or more widely</i></p>
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			<p><i>meshed grafts incurs an increased risk of graft loss but that the addition of ReCell mitigates this increased risk. They suggest that the additional application of ReCell to a thin meshed graft will reduce the persistence of the mesh pattern in the healed skin, reduce the risk of graft failure and therefore allow wider meshing to be used more routinely which will reduce the donor site areas required.”</i></p>
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Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
<p>In lines 4-6 of the final paragraph on page 16 (Cost</p>	<p>Reword sentence as: <i>The burn wound in the base case model was defined as</i></p>	<p>Simple factual error. Each kit can process a biopsy of up to</p>	<p>This was a typographical error. The text will be changed as</p>

<p>analysis) the EAC states that the base-case wound size of 640cm² represents the maximum treatment area for a single ReCell kit. In fact it represents the maximum treatment area for two ReCell kits</p>	<p><i>partial thickness with no definite areas of deep involvement and an area of 640cm² (the maximum treatment area for two ReCell kits)</i></p>	<p>4cm² and cover an area of 80 times this amount = 320cm²</p>	<p>requested. The EAC thanks the sponsor for noting this.</p>
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Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
<p>In the last paragraph on page 12, the second sentence states: <i>“No mention of indeterminate thickness burns is made, suggesting that the use of ReCell should be delayed</i></p>	<p>Delete this sentence</p>	<p>In paragraph 3.3 the care pathway states that step 1 is the clinical assessment of depth at 0-2 days. Further on in this section, in paragraph 5, we then state: <i>“For patients with partial thickness burns,</i></p>	<p>This section refers solely to the Decision Problem in the final scope, where no mention of indeterminate burns is made. The text will be altered to make this clearer.</p>

<p><i>until definitive wound assessment is possible, either following several days wait or using the moorLDI2 Burns imager (NICE 2011)”</i></p> <p>In fact there is clear discussion of the role of ReCell in indeterminate depth burns – indeed this is one of its key indications</p>		<p><i>or those of indeterminate depth, harvested cells can be applied using ReCell at step 1, in order to maximise the chances of a wound re-epithelialising.”</i> This assumption then goes on to form the basis of the economic modelling.</p>	<p><i>“No mention of indeterminate thickness burns is made in the Decision Problem, suggesting that the intention in the scope was that use of ReCell should be delayed until definitive wound assessment is possible, either following several days wait or using the moorLDI2 Burns imager (NICE 2011)”</i></p> <p>Note that in sections 9.1.3 and 9.1.5 of the sponsor’s submission the indication for the economic model is not described as an indeterminate depth burn. This is discussed in the ‘Patients’ section of 4.2 in the Assessment Report (p48).</p>
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Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
<p>Related to the previous point (Issue 3) in the first paragraph on page 10, the EAC discuss that we have not mentioned the use of a burn depth imager at day 2-5. As ReCell will be used from day 0-2, this is not relevant</p>	<p>Change the sentence that reads: <i>“However, the sponsor has not referred to the use of the moorLDI2 Burn Imager in their submission”</i> to read: <i>“The sponsor has not referred to the use of the moorLDI2 Burn Imager in their submission, as it falls outside the timescale envisaged for the use of ReCell at step 1”</i></p>	<p>See rationale for Issue 3 above</p>	<p>The moorLDI2 Burns Imager is recommended by NICE for use in indeterminate depth burns (MTG2) and should be used between 2-5 days post-injury. Indeterminate burns are not mentioned in the ReCell scope. If the sponsor wants ReCell to be evaluated in the context of indeterminate burns they should explain how this fits in with existing guidelines. If the use of ReCell in these injuries is incompatible with the use of moorLDI2 then MTAC should be made aware of this.</p>

			<p>The suggested sentence indicates that the EAC knows why the moorLDI2 was not referred to, which is not the case. The existing text has been retained and an additional sentence appended to the paragraph: “<i>The sponsor indicates that in such cases ReCell would be applied at 0-2 days post-injury.</i>”</p>
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Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
<p>On page 67, under “Claimed benefits for the patient” the EAC states that benefits relating to donor site healing fall outside the scope and</p>	<p>There needs to be an acknowledgement that this can legitimately be considered to be within scope, albeit one not assessed by the</p>	<p>Discussion between Caroline Hall, Bernice Dillon, Jonathan Belsey and Sue Pierce on 22/8/13</p>	<p>This is not a factual inaccuracy because it is an interpretation of the scope arrived at jointly between the EAC and the MTEP team. Discussions at the</p>

<p>have therefore not been considered. In our joint teleconference on 22nd August 2013, this issue was discussed and it was the opinion of NICE that a broad interpretation should be given and that data on donor site healing should be considered to be within the scope.</p>	EAC		teleconference cannot be used to justify a factual amendment.
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical Technologies Evaluation Programme

MT 205 - The ReCell spray-on skin system for treating skin loss, scarring and depigmentation after burn injury

Expert Adviser Questionnaire Responses

Name of Expert Advisers	Job Title	Professional Organisation/ Specialist Society	Nominated by	Ratified
Dr Amber Young	Lead Paediatric Burns Anaesthetist and Paediatric Burns Network Lead	Association of Burns & Reconstructive Anaesthetists	Specialist Society	-
Mr Bruce Philp	Consultant Plastic Surgeon	British Burn Association	Sponsor	Y
Dr Rebecca Martin	Lead Anaesthetist & Intensivist	Association of Burns & Reconstructive Anaesthetists	Specialist Society	-
Miss Isabel Jones	Burns Consultant	British Association of Plastic, Reconstructive and Aesthetic Surgeons	Sponsor	Y
Dr Sarah Pape	Consultant Plastic Surgeon	British Association of Plastic, Reconstructive and Aesthetic Surgeons	NICE	-

YOUR PERSONAL EXPERIENCE (IF ANY) WITH THIS TECHNOLOGY

Question 2: Please indicate your experience with this technology?

Expert Advisers	I have had direct involvement with this	I have referred patients for its use	I manage patients on whom it is used in another part of their care pathway	I would like to use this technology but it is not currently available to me
Dr Amber Young Lead Paediatric Burns Anaesthetist and Paediatric Burns Network Lead	Yes	No	Yes	No
Mr Bruce Philp Consultant Plastic Surgeon	Yes	Yes	Yes	No
Dr Rebecca Martin Lead Anaesthetist & Intensivist	Blank	Blank	Yes	Blank
Miss Isabel Jones Burns Consultant	Yes	No	No	No
Dr Sarah Pape Consultant Plastic Surgeon	No	No	No	Yes
<i>Any Comments?</i>				
Dr Amber Young Lead Paediatric Burns Anaesthetist and Paediatric Burns Network Lead	Blank			
Mr Bruce Philp Consultant Plastic Surgeon	I have used Recell spray cells for my burns patients for over 4 years. Recell is used on our burns unit for a number of indications which are detailed below. It is a unique technology at the moment, with potentially important patient and health care resource benefits.			
Dr Rebecca Martin Lead Anaesthetist & Intensivist	I provide anaesthesia and intensive care to patients who have received and may benefit from this technology and am involved as part of a specialist team caring for patients with burns to whom it is applicable.			

Expert Advisers	I have had direct involvement with this	I have referred patients for its use	I manage patients on whom it is used in another part of their care pathway	I would like to use this technology but it is not currently available to me
Miss Isabel Jones Burns Consultant	Blank			
Dr Sarah Pape Consultant Plastic Surgeon	I have received training from the manufacturer but refused permission to use in my hospital because of costs			

Question 3: Have you been involved in any kind of research on this technology? If Yes, please describe?

Expert Advisers	Yes/No	Comment
Dr Amber Young Lead Paediatric Burns Anaesthetist and Paediatric Burns Network Lead	No	Blank
Mr Bruce Philp Consultant Plastic Surgeon	No	I have not been involved in formal research yet but am keen to be involved in clinical trials using Recell in the future. A research project comparing Recell and cultured allogeneic cells in suspension (produced by Altrika) on burn wounds is due to start in our unit later in 2013.
Dr Rebecca Martin Lead Anaesthetist & Intensivist	No	Blank
Miss Isabel Jones Burns Consultant	Yes	Blank
Dr Sarah Pape Consultant Plastic Surgeon	No	Blank

THIS PRODUCT (TECHNOLOGY) AND ITS USE

Question 4: How would you best describe this technology?

Expert Advisers	It is a minor variation on existing technologies with little potential for different outcomes and impact	It is a significant modification of an existing technology with real potential for different outcomes and impact	It is thoroughly novel - different in concept and/ or design to any existing
Dr Amber Young Lead Paediatric Burns Anaesthetist and Paediatric Burns Network Lead	No	Yes	Yes
Mr Bruce Philp Consultant Plastic Surgeon	No	No	Yes
Dr Rebecca Martin Lead Anaesthetist & Intensivist	Blank	Blank	Yes
Miss Isabel Jones Burns Consultant	Blank	Yes	Blank
Dr Sarah Pape Consultant Plastic Surgeon	No	Yes	No
<i>Any Comments?</i>			
Dr Amber Young Lead Paediatric Burns Anaesthetist and Paediatric Burns Network Lead	Blank		
Mr Bruce Philp Consultant Plastic Surgeon	The technology is novel and unique and there are no current comparator products that I am aware of. The technique of enzymatic preparation of an autologous cell suspension is not new but the Recell kit allowing preparation in the operating theatre of an autologous skin cell suspension is new and unique.		
Dr Rebecca Martin Lead Anaesthetist & Intensivist	Previous techniques have relied on laboratory culture of patients skin cells which is time consuming and can only be performed in a limited number of specialist laboratories; this technology can be applied at the time of initial surgery without additional delays and expense of laboratory cultured cells		

Miss Isabel Jones Burns Consultant	Blank
Dr Sarah Pape Consultant Plastic Surgeon	Blank

Question 5: What is the most appropriate use (e.g. clinical indication) for the technology?

Expert Advisers	Comment
Dr Amber Young Lead Paediatric Burns Anaesthetist and Paediatric Burns Network Lead	It is used to improve wound healing in burn patients both in burn wounds and donor sites. It is especially useful in larger or difficult to heal burns / wound areas with or without skin grafts with or without wider spaced meshing.

Expert Advisers	Comment
<p>Mr Bruce Philp Consultant Plastic Surgeon</p>	<p>Recell has a role to play in a number of clinical scenarios in burn care.</p> <ol style="list-style-type: none"> 1. Mid and deep dermal burns - To transplant autologous keratinocytes and melanocytes to augment and speed healing in mid - to deep dermal burns. This can prevent the need for autologous skin grafting. Recell is usually used following debridement using the Versajet hydrosurgery system and Biobrane dressings. The donor site for the Recell cell suspension is very small compared to conventional skin grafting techniques. There may even be a role in healing superficial burns in selected cases (particularly in children) as there is some limited evidence of possible supra normal healing times using autologous cell suspensions. 2. Patients with pigmented skin types (Fitzpatrick skin type 3-6) - Recell uniquely can reintroduce melanocytes into healing burn wounds in patients with pigmented skin types, hence reducing or preventing hypo-pigmented burn scars. There is now convincing evidence of persistent melanocyte transplantation using Recell in vitiligo patients and our anecdotal evidence supports melanocyte transplantation and improved repigmentation in burn wounds. 3. Recell can augment healing of meshed skin grafts by accelerating the healing of the mesh graft interstices. The aesthetic appearance of meshed grafts plus Recell also seems improved. 4. Skin Graft donor sites - Recell may reduce the healing time of donor sites, which is particularly important in major burn injuries when skin graft donor site healing is the main rate limiting step in burn wound closure 5. Numerous studies have shown a relationship with slow time-to-healing of burns and the resultant incidence in hypertrophic scars (red, lumpy and itchy/painful scars) .A reduction in the healing time of burn wounds, meshed skin grafts and donor sites treated with Recell may reduce the incidence of hypertrophic scarring and the associated adverse symptoms and use of resources (scar management therapy including pressure garments, splints, silicone dressings, physiotherapy etc.)
<p>Dr Rebecca Martin Lead Anaesthetist & Intensivist</p>	<p>Our team has used this in management of acute burn injuries to aid burn wound healing of partial thickness burn injuries eg scald burns in children. We have also used with meshed skin grafts to improve time to healing, reduction and improved healing of donor sites in major burns. Timely healing of injuries reduces the incidence of hypertrophic scarring and improves outcomes, and prompt donor site healing allows re-harvesting of door sites which allows timelier coverage and reduced risk of infection in major burn patients.</p> <p>It can be additionally applied to reconstructive surgery and used to improve established scar appearance .</p>

Expert Advisers	Comment
Miss Isabel Jones Burns Consultant	This technology is used to apply a suspension of autologous epidermal cells to wounds. It has varied applications including -on a chronic wound with the aim of changing the molecular profile and stimulating epithelialisation -on a partial thickness injury that will struggle to heal without a graft -on stable depigmented skin
Dr Sarah Pape Consultant Plastic Surgeon	Resurfacing of mid to deep-dermal burns for quicker healing and less scarring, repigmentation of depigmented skin in scars and vitiligo

COMPARATORS (including both products in current routine use and also “competing products”)

Question 6: Given what you stated is the appropriate indication (clinical scenario) for its use, what are the most appropriate "comparators" for this technology which are in routine current use in the NHS?

Expert Advisers	Comment
Dr Amber Young Lead Paediatric Burns Anaesthetist and Paediatric Burns Network Lead	Other skin healing products such as split thickness skin grafts for full thickness/ deep dermal wounds and biological dressings for partial thickness scalds and donor sites with traditional dressings .
Mr Bruce Philp Consultant Plastic Surgeon	There are no direct comparator products that I am aware of. Appropriate comparators would be standard-of-care treatments for a particular burns unit such as particular dressings or skin grafting. Cultured keratinocytes are rarely used in our unit (only in massive burn injury- burns greater than 75% TBSA- in children and young adults). We previously had access to sub-confluent keratinocyte cell culture through a research link to the Royal London Hospital but that facility has not been available for the last 3 years. As far as I am aware cultured keratinocytes are currently only commercially available from Altrika in Sheffield, UK (Myskin and allogeneic Cryoskin) but these cell delivery systems are very different to Recell; Myskin is autologous keratinocytes grown in the laboratory on a silicone and acrylic sheet and Cryoskin uses allogeneic cells grown on a silicone sheet.
Dr Rebecca Martin Lead Anaesthetist & Intensivist	one in routine use but occasional use of laboratory cultured keratinocytes, but this technology is not readily or locally available
Miss Isabel Jones Burns Consultant	The only comparator is laboratory processing of a skin biopsy to release the keratinocytes for use immediately in suspension, or following culture. The indications are similar, but Recell has the very significant advantage of being available anywhere without requiring the use of a laboratory able to process human tissue for clinical use.
Dr Sarah Pape Consultant Plastic Surgeon	Dressings, skin graft, cosmetic camouflage make-up

Question 7: "Competing products": Are you aware of any other products which have been introduced with the same purpose as this one?

Expert Advisers	Comment
Dr Amber Young Lead Paediatric Burns Anaesthetist and Paediatric Burns Network Lead	As above- but none specifically
Mr Bruce Philp Consultant Plastic Surgeon	I am not aware of any competing products. Various commercial companies have offered cultured keratinocytes for use in burns in the last 30 years but there are no other products that I am aware of with the same purpose as Recell, which is the preparation and delivery of non-cultured dissociated skin cells to the burn wound.
Dr Rebecca Martin Lead Anaesthetist & Intensivist	not aware
Miss Isabel Jones Burns Consultant	No
Dr Sarah Pape Consultant Plastic Surgeon	No

POSSIBLE BENEFITS FOR PATIENTS

Question 8: What are the likely additional benefits for patients of using this technology, compared with current practice/comparators?

Expert Advisers	Comment
Dr Amber Young Lead Paediatric Burns Anaesthetist and Paediatric Burns Network Lead	Potential for improved healing for difficult to heal or large burn areas with or without widely meshed grafts and improved donor site healing. Improved healing in partial thickness scalds. Improved speed and quality of healing as above resulting in decreased length of stay, decreased critical care stay, decreased scarring, improved quality of healing, decreased septic episodes.
Mr Bruce Philp Consultant Plastic Surgeon	1. Faster wound healing times for burn wounds, meshed grafts and skin graft donor sites. This may result in reduced length of hospital stay, reduced use of medical, nursing and therapy resources (dressings, analgesia, in-patient and out-patient therapies etc.) 2. Reduction in hypertrophic scarring and associated morbidity (pain, itch, reduced function and range of movement, psycho-social) and the associated treatment modalities including physio-therapy and occupational therapy, pressure garments, scar management products etc. 3. Repigmentation of burn wounds in patients with pigmented skin . that normally would result in hypopigmentation. 4. Faster rehabilitation and return to work/school/normal activities of daily living as a result of faster healing, reduced wound related symptoms and reduced scarring.
Dr Rebecca Martin Lead Anaesthetist & Intensivist	Reduced time to wound healing, benefits in appearance of scars and pigmentation loss following burns; enables the use of the patients own skin cells at the time of surgery to assist healing in a timely and accessible technology and opens the technology to many more patients then previously possible using laboratory cultured cells
Miss Isabel Jones Burns Consultant	This makes a technique currently available only to a handful of hospitals allied to a human cell culture lab available in any clinical setting. Keratinocytes applied in this way have been demonstrated to aid re-epithelialisation of burns wounds and repigmentation of depigmented areas.
Dr Sarah Pape Consultant Plastic Surgeon	Better appearance of scars

Question 8.1: Is each additional benefit likely to be realised in practice? What are the likely obstacles?

Expert Advisers	Comment
Dr Amber Young Lead Paediatric Burns Anaesthetist and Paediatric Burns Network Lead	Yes. The obstacles relate to cost, technical ease of use and the evidence base.
Mr Bruce Philp Consultant Plastic Surgeon	Yes. No obstacles assuming the product is funded and available.
Dr Rebecca Martin Lead Anaesthetist & Intensivist	Donor site and burn wound healing is multifactorial and also depends upon clinical status of patient and any episodes infection. Any technology that assists healing and time to burn wound coverage impacts on survival from major injuries. Improved cosmetic and functional outcomes after burns are related to time to healing with prolonged healing time associated with hypertrophic scars.
Miss Isabel Jones Burns Consultant	The primary obstacle to use is funding and cost
Dr Sarah Pape Consultant Plastic Surgeon	Yes. Obstacle is mainly cost and need for general anaesthetic

Question 8.2: *How might these benefits be measured? What specific outcome measures would enable assessment of whether additional benefits for patients are being realised?*

Expert Advisers	Comment
Dr Amber Young Lead Paediatric Burns Anaesthetist and Paediatric Burns Network Lead	Benefits could be measured as: time to full or 95% healing, scarring as measured at 6 months, 12 and 24 months (using VAS and/or POSAS scar tools), incidence of wound infection (as defined by the American Burn association criteria) and hospital length of stay. Cost will need to be assessed in relation to patient benefit in relation to healing, scarring, survival and length of hospital stay.
Mr Bruce Philp Consultant Plastic Surgeon	Reduction in length of stay in hospital, improved quality of life outcomes (pain, reduced scarring, improved pigmentation), reduced dressings and therapy requirements.
Dr Rebecca Martin Lead Anaesthetist & Intensivist	Simple measures of time to burn wound healing, reduction of time in dressings post surgery, reduced analgesic requirements as wounds heal, incidence of hypertrophic scarring, need for future scar management
Miss Isabel Jones Burns Consultant	Adequately powered clinical trials could provided conclusive evidence of improved epithelialisation, wound healing and repigmentation. The outcome measures would include size of wound, time to healing, scarring and pigmentation evaluation
Dr Sarah Pape Consultant Plastic Surgeon	Time to healing, Scar quality (Vancouver scar assessment scale or similar. Skin colour - spectrophotometry

Question 8.3: *How good is this evidence for each of these additional benefits?*

Expert Advisers	Comment
Dr Amber Young Lead Paediatric Burns Anaesthetist and Paediatric Burns Network Lead	I am not aware that there is good evidence but I have not done a full literature search.
Mr Bruce Philp Consultant Plastic Surgeon	There is increasing published evidence (see below) and we have anecdotal evidence from our own burn service.
Dr Rebecca Martin Lead Anaesthetist & Intensivist	Established evidence that time to wound healing effects incidence of hypertrophic scarring. Literature predominantly has case series of benefits of the use of ReCell technology. The use of the technology is widening to improve scarring from multiple causes

Expert Advisers	Comment
Miss Isabel Jones Burns Consultant	There are a number of case reports and pilot series but no RCT.
Dr Sarah Pape Consultant Plastic Surgeon	Don't understand the question

Question 8.4: Please add any further comment on the claimed benefits of the technology to patients, as you see applicable

Expert Advisers	Comment
Dr Amber Young Lead Paediatric Burns Anaesthetist and Paediatric Burns Network Lead	Blank
Mr Bruce Philp Consultant Plastic Surgeon	Blank
Dr Rebecca Martin Lead Anaesthetist & Intensivist	Improved pigmentation and colour match in healing burn wounds. There is no significant impact on the time required in theatre or length of anaesthetic in a well planned procedure.
Miss Isabel Jones Burns Consultant	Improved healing of difficult wound should reduce the requirement for out patient dressings
Dr Sarah Pape Consultant Plastic Surgeon	Blank

POSSIBLE BENEFITS FOR THE HEALTHCARE SYSTEM

Question 9: *What are the likely additional benefits for the healthcare system of using this technology, compared with current practice/comparators?*

Expert Advisers	Comment
Dr Amber Young Lead Paediatric Burns Anaesthetist and Paediatric Burns Network Lead	Potential for improved speed and quality of healing, decreased length of stay, decreased critical care stay, decreased scarring, decreased septic episodes. Decreased scar management requirement. Decrease in antibiotic use and thus bacterial resistance. Therefore improved clinical and cost effectiveness
Mr Bruce Philp Consultant Plastic Surgeon	Reduced length of stay in hospital and therefore reduced associated medical, nursing, therapy and administrative costs. Reduced dressings, pain relief medication etc.
Dr Rebecca Martin Lead Anaesthetist & Intensivist	Accelerated wound healing can reduce hospital length of stay following burn injury and the number of hospital episodes for dressing wounds. If better cosmetic outcomes are achieved at initial surgery this may reduce the long term need for further consultations/ surgery to improve scar appearance and improved psychosocial outcomes from burn injury.
Miss Isabel Jones Burns Consultant	Decrease time to healing reduces the need for time-consuming and expensive specialised dressings and improves the long term scar appearance and function. Healing/improved chronic wounds decreases pain, repigmentation is of psychological benefit.
Dr Sarah Pape Consultant Plastic Surgeon	Fewer patients with long-term psychological distress about scars and skin depigmentation

Question 9.1: *Is each additional benefit likely to be realised in practice? What are the likely obstacles?*

Expert Advisers	Comment
Dr Amber Young Lead Paediatric Burns Anaesthetist and Paediatric Burns Network Lead	Yes. Obstacles relate to clinical trials (and length of these to assess scar formation), professional dissemination and agreement in achieving national policy which is lacking in burn care.
Mr Bruce Philp Consultant Plastic Surgeon	Yes

Expert Advisers	Comment
Dr Rebecca Martin Lead Anaesthetist & Intensivist	This will depend on good departmental protocols for the appropriate use of the technology and care pathways for patients receiving this technology. The longer term goals of reduced need for recurrent interventions either physiological or psychological for poor scarring will depend on patient perception and expectation of burn surgery as technology develops.
Miss Isabel Jones Burns Consultant	Primary obstacle is cost of kit, and being re-imbursed
Dr Sarah Pape Consultant Plastic Surgeon	Yes

Question 9.2: How might these benefits be measured? What specific outcome measures would enable assessment of whether additional benefits for the healthcare system are being realised?

Expert Advisers	Comment
Dr Amber Young Lead Paediatric Burns Anaesthetist and Paediatric Burns Network Lead	Benefits could be measured as: time to full or 95% healing, scarring as measured at 6 months, 12 and 24 months (using VAS and/or POSAS scar tools), incidence of wound infection and hospital length of stay.
Mr Bruce Philp Consultant Plastic Surgeon	Length of stay in hospital, time to healing and discontinuation of dressings, analgesic requirements, scar outcomes including pigmentation, time of return to work/normal activities. Cost benefit analysis of standard care versus use of Recell. Length of stay is relatively easy to measure whilst the other quality of life measurements are more difficult.
Dr Rebecca Martin Lead Anaesthetist & Intensivist	Scarring after burn injury can be measure by various scoring systems. Requirement for number of dressing clinic visits. Psychological well being in dependent not just on size and appearance of scars so may be difficult to measure
Miss Isabel Jones Burns Consultant	Cost analysis of kit & procedure vs prolonged dressing changes, monitoring of analgesia requirements, POSAS/Vancouver scar scales, scar pain, scar revision rates, digital evaluation of repigmentation
Dr Sarah Pape Consultant Plastic Surgeon	QoL, anxiety and depression scales

Question 9.3: How good is this evidence for each of these additional benefits?

Expert Advisers	Comment
<p>Dr Amber Young Lead Paediatric Burns Anaesthetist and Paediatric Burns Network Lead</p>	<p>I am not aware that there is good evidence for these but I have not done a full literature search.</p>
<p>Mr Bruce Philp Consultant Plastic Surgeon</p>	<p>Limited published data (see references below) and clinical trials (Ref 1 & 4 below) , presentation data from other users at symposia, personal/ and departmental anecdotal evidence. References: 1) Wood F, et al. A prospective randomised clinical pilot study to compare the effectiveness of Biobrane1 synthetic wound dressing, with or without autologous cell suspension, to the local standard treatment regimen in paediatric scald injuries. Burns (2012), doi:10.1016/j.burns.2011.12.020. 2)Wood F. Clinical potential of autologous epithelial suspension. Wounds 2003;15. 3)Wood F, Kolybaba ML, Allen P. The use of cultured epithelial autograft in the treatment of major burn wounds: eleven years of clinical experience. Burns 2006;32:538–44. 4)A randomized trial comparing ReCell system of epidermal cells delivery versus classic skin grafts for the treatment of deep partial thickness burns. Gravante G, Di Fede MC, Araco A, Grimaldi M, De Angelis B, Arpino A, Cervelli V, Montone A. Burns. 2007 Dec;33(8):966-72.</p>
<p>Dr Rebecca Martin Lead Anaesthetist & Intensivist</p>	<p>Long term healthcare benefits difficult to establish as until the bedside technology was available use of culture cells was a very limited in use.</p>
<p>Miss Isabel Jones Burns Consultant</p>	<p>see 8.3</p>
<p>Dr Sarah Pape Consultant Plastic Surgeon</p>	<p>Don't know</p>

Question 9.4: Please add any further comment on the claimed benefits of the technology to the healthcare system, as you see applicable

Expert Advisers	Comment
Dr Amber Young Lead Paediatric Burns Anaesthetist and Paediatric Burns Network Lead	Blank
Mr Bruce Philp Consultant Plastic Surgeon	A reduction in symptomatic scarring may result in reduced requirement for reconstructive surgery and the associated expenses. Improved burn scar and repigmentation will reduce adverse psychological sequelae. A faster return to employment/schooling will increase societal benefits.
Dr Rebecca Martin Lead Anaesthetist & Intensivist	Blank
Miss Isabel Jones Burns Consultant	Blank
Dr Sarah Pape Consultant Plastic Surgeon	Blank

FACILITIES, TRAINING AND FUNCTIONING

Question 10: *Are there any particular facilities or infrastructure which needs to be in place for the safe and effective use of this technology?*

Expert Advisers	Comment
Dr Amber Young Lead Paediatric Burns Anaesthetist and Paediatric Burns Network Lead	Not as far as I am aware
Mr Bruce Philp Consultant Plastic Surgeon	Training is required to use the Recell kit . This is currently provided free of charge by the company. No other special infrastructure or facilities is required (only the refrigerator storage of the enzyme trypsin and the storage space for the other components of the kit. Other requirements are standard of care in burns surgery (wound debridement, skin graft harvest equipment, wound dressings etc).
Dr Rebecca Martin Lead Anaesthetist & Intensivist	The technology is easy to learn to use so training of theatre scrub teams and surgeons is straightforward and easy to support.
Miss Isabel Jones Burns Consultant	Access to operating theatres/clean procedures room
Dr Sarah Pape Consultant Plastic Surgeon	Individual training. Appropriate storage

Question 11: *Is special training required to use this technology safely and effectively?*

Expert Advisers	Comment
Dr Amber Young Lead Paediatric Burns Anaesthetist and Paediatric Burns Network Lead	Not as far as I am aware
Mr Bruce Philp Consultant Plastic Surgeon	Yes although the technique is relatively easy to master and the kit has clear instructions.
Dr Rebecca Martin Lead Anaesthetist & Intensivist	The kits are easy to use once initial training has occurred.

Miss Isabel Jones Burns Consultant	Yes
Dr Sarah Pape Consultant Plastic Surgeon	Yes

Question 12: Please comment on any issues relating to the functioning, reliability and maintenance of this technology which may be important to consider if it is introduced

Expert Advisers	Comment
Dr Amber Young Lead Paediatric Burns Anaesthetist and Paediatric Burns Network Lead	Blank
Mr Bruce Philp Consultant Plastic Surgeon	The ReCellis reliable and single use
Dr Rebecca Martin Lead Anaesthetist & Intensivist	Single patient off the shelf kit so reliability of each kit is maintained.
Miss Isabel Jones Burns Consultant	Single use kit, consistently reliable to use
Dr Sarah Pape Consultant Plastic Surgeon	Don't know. Haven't used it yet

COSTS

Question 13: Please provide any comments on the likely cost consequences of introducing this technology. In particular, please comment on the implications of this technology replacing the comparator/s you have described above

Expert Advisers	Comment
Dr Amber Young Lead Paediatric Burns Anaesthetist and Paediatric Burns Network Lead	I am not able to do this as I do not have the costs of Recell available. If speed of and quality of healing is improved, cost savings to the NHS are likely to be significant both in terms of length of hospital stay, scar management and antibiotic use.
Mr Bruce Philp Consultant Plastic Surgeon	The cost per unit is about £950 + VAT but cost savings are possible as the company offers a reduction in cost per unit the greater the number of purchased . There is some published data showing a reduction in overall costs of burn care with Recell use (Ref 1 above).
Dr Rebecca Martin Lead Anaesthetist & Intensivist	Previous culture skin technologies involved sending skin cells for incubation in specialist licensed laboratories and success with the samples in clinical use was unpredictable. It was time consuming and expensive and required specialist transport of the cells. ReCell is a kit designed to be use at the bedside in theatre to harvest, treat and deliver cells and does not require these expenses and time delays. This makes use of this technology more accessible to all patients who may benefit.
Miss Isabel Jones Burns Consultant	The initial cost of the kit would be offset by the advantage in speeding up healing and improved scarring
Dr Sarah Pape Consultant Plastic Surgeon	Don't know. Cost of equipment plus training

GENERAL ADVICE BASED ON YOUR SPECIALIST KNOWLEDGE

Question 14: *Is there controversy about any aspect of this technology or about the care pathway?*

Expert Advisers	Comment
Dr Amber Young Lead Paediatric Burns Anaesthetist and Paediatric Burns Network Lead	There is no national guidance or professional agreement about when or in which patients to use this technology as far as I am aware.
Mr Bruce Philp Consultant Plastic Surgeon	Given the recognised difficulty in evaluating outcomes and the effect of specific interventions in burn care (because of the multi-factorial nature of the injuries, patients and multiple treatment modalities) the accurate assessment of the impact of the technology is difficult. None the less the science is plausible (see references below) and the clinical results (our own experience and that of others documented in the literature and presented at symposia) appear to support the beneficial use of the technology. References: 1) Characterisation of the cell suspension harvested from the dermal epidermal junction using a ReCell® kit. Wood FM, Giles N, Stevenson A, Rea S, Fear M. Burns. 2012 Feb;38(1):44-51. 2) Cultured autologous keratinocytes in suspension accelerate epithelial maturation in an in vivo wound model as measured by surface electrical capacitance. Magnusson M, Papini RP, Rea SM, Reed CC, Wood FM. Plast Reconstr Surg. 2007 Feb;119(2):495-9.
Dr Rebecca Martin Lead Anaesthetist & Intensivist	no
Miss Isabel Jones Burns Consultant	No
Dr Sarah Pape Consultant Plastic Surgeon	Not as far as I am aware

Question 15: *If NICE were to develop guidance on this technology, how useful would this be to you and your colleagues?*

Expert Advisers	Comment
Dr Amber Young Lead Paediatric Burns Anaesthetist and Paediatric Burns Network Lead	Extremely useful
Mr Bruce Philp Consultant Plastic Surgeon	Very useful
Dr Rebecca Martin Lead Anaesthetist & Intensivist	NICE technology approval would support our continued use of the technology in appropriate patient groups to improve outcomes from burn injuries.
Miss Isabel Jones Burns Consultant	Very, in supporting funding for standard application of Recell
Dr Sarah Pape Consultant Plastic Surgeon	Moderately overall but significant for selected patients

Question 16: *Do any subgroups of patients need special consideration in relation to the technology (for example, because they have higher levels of ill health, poorer outcomes, problems accessing or using treatments or procedures)? Please explain why*

Expert Advisers	Comment
Dr Amber Young Lead Paediatric Burns Anaesthetist and Paediatric Burns Network Lead	The largest group of children's burns are partial thickness scalds. An understanding of how this technology would impact on healing with this group of patients would impact on many children each year.
Mr Bruce Philp Consultant Plastic Surgeon	Patients with pigmented skin types. The results of scar pigmentary change in these patients is currently very difficult to treat except by camouflage techniques (clothing, makeup and limited role of cosmetic tattooing).
Dr Rebecca Martin Lead Anaesthetist & Intensivist	No

Miss Isabel Jones Burns Consultant	Diabetic and vascular patients would benefit from treatment to chronic ulcers, burns patients benefit because of the extent and complexity of their wounds and scars.
Dr Sarah Pape Consultant Plastic Surgeon	Patients with skin of colour

CONFLICTS OF INTEREST

Question 18.1: Do you or a member of your family have a personal pecuniary interest? The main examples are as follows:

Expert Advisers	Consultancies or directorships	Fee-paid work	Shareholdings	Expenses and hospitality	Investments	Personal non-pecuniary interest
Dr Amber Young Lead Paediatric Burns Anaesthetist and Paediatric Burns Network Lead	No	No	No	No	No	Yes
Mr Bruce Philp Consultant Plastic Surgeon	No	No	No	Yes	No	No
Dr Rebecca Martin Lead Anaesthetist & Intensivist	No	No	No	No	No	No
Miss Isabel Jones Burns Consultant	No	No	No	No	No	No
Dr Sarah Pape Consultant Plastic Surgeon	No	No	No	No	No	No

If you have answered YES to any of the above statements please describe the nature of the conflict(s) below.

Dr Amber Young Lead Paediatric Burns Anaesthetist and Paediatric Burns Network Lead	I am deputy chair of the British Burns Association and Chair of the Burn Care Clinical Reference Group. Both groups have a direct interest in national burn care policy and guidelines.
--	---

Mr Bruce Philp Consultant Plastic Surgeon	I have been funded to attend a symposium on Recell use in burns and for other indications (vitiligo, chronic wounds, aesthetic etc.) in Munich, Germany in March 2013. The company, Avita Medical, paid for my travel expenses, hotel accommodation and meals. This was probably "reasonably required" in that none of these expenses were excessive or luxurious but I feel that I should declare this support for the sake of transparency and probity.
Dr Rebecca Martin Lead Anaesthetist & Intensivist	Blank
Miss Isabel Jones Burns Consultant	Blank
Dr Sarah Pape Consultant Plastic Surgeon	Blank

Question 18.2: Do you have a non-personal interest? The main examples are as follows:

Expert Advisers	Fellowships endowed by the healthcare industry	Support by the healthcare industry or NICE that benefits his/her position or department, e.g. grants, sponsorship of posts
Dr Amber Young Lead Paediatric Burns Anaesthetist and Paediatric Burns Network Lead	No	No
Mr Bruce Philp Consultant Plastic Surgeon	No	No
Dr Rebecca Martin Lead Anaesthetist & Intensivist	No	No
Miss Isabel Jones Burns Consultant	No	No
Dr Sarah Pape Consultant Plastic Surgeon	No	No

If you have answered YES to any of the above statements please describe the nature of the conflict(s) below.

Dr Amber Young Lead Paediatric Burns Anaesthetist and Paediatric Burns Network Lead	Blank
Mr Bruce Philp Consultant Plastic Surgeon	Blank
Dr Rebecca Martin Lead Anaesthetist & Intensivist	Blank
Miss Isabel Jones Burns Consultant	Blank
Dr Sarah Pape Consultant Plastic Surgeon	Blank



Cedar

Healthcare Technology Research Centre

External Assessment Centre Report:

The ReCell spray-on skin system for
treating skin loss, scarring and
depigmentation after burn injury

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CYMRU
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WALES

Bwrdd Iechyd Prifysgol
Caerdydd a'r Fro
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Declared interests of the authors

None.

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Alison Weightman, Support Unit for Research Evidence (SURE), Information Services, Cardiff University

Rider on responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.



Abbreviations

COD	Change of dressing
GA	General anaesthetic/anaesthesia
HRG	Health resource group
iBID	International Burn Injury Database
LOS	Length of (hospital) stay
PbR	Payment by Results
RCT	Randomised control trial
SSG	Split thickness skin graft
STDG	Split thickness dermal graft
TBSA	Total burn surface area (given as %)
VAS	Visual analogue scale
VSS	Vancouver scar scale - a multivariable scale that includes assessment of vascularity (0-3), pigmentation (0-2), pliability (0-5) and height (0-3). Normal skin would have a value of 0 and the maximum value is 13.



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1 Summary

Scope of the sponsor's submission

There are two groups of patient population, intervention and comparator defined in the Decision Problem corresponding to partial thickness burns and larger and/or deeper burn injuries. The sponsor did not address these two groups separately. They have collated evidence for the use of ReCell in all acute burns and described each study separately. This is an appropriate approach given the heterogeneity of burn injuries and treatment modalities and the difficulty of separating these into specific groups. There is difficulty with the multiple terms used to describe burn injuries and the ways in which these have been grouped, in the published evidence, the communication with advisers and the economic modelling. The sponsor has additionally included evidence for pigmentation outcomes following the use of ReCell in hypopigmented scars and vitiligo. This data has been excluded as outside the scope, as has additional data on the use of ReCell to treat skin graft donor sites.

Summary of clinical evidence submitted by the sponsor

The sponsor's summary of the clinical evidence is that ReCell is at least as effective as split thickness skin graft (SSG) in the treatment of partial thickness burns in terms of wound healing and scar outcomes. They further note no known device-related adverse events and no greater risk of wound infection or graft loss with respect to SSG. The sponsor also states that ReCell plus SSG or dermal grafts allows more rapid healing than SSG alone, and that ReCell plus Biobrane provides faster healing than SSG, along with reduced costs and shorter hospital stay. The sponsor notes that the use of ReCell plus Biobrane is not demonstrated to be superior to either ReCell alone or Biobrane alone.

Summary critique of clinical evidence submitted by the sponsor

The sponsor described an appropriate main search strategy and submitted 3 peer-reviewed journal articles and 8 conference abstracts. Two conference abstracts were deemed outside the scope by the EAC. The EAC additionally identified another 9 conference abstracts, 2 of which were unavailable and another 5 of which contained data that overlapped with references in the sponsor's submission. These additional references did not add substantially to the available clinical evidence due to low levels of detail in the available abstracts.

The EAC concurs with the sponsor's conclusion regarding the comparative clinical effectiveness between ReCell and SSG. We also agree that there is no evidence of additional clinical benefit from the addition of ReCell to Biobrane in comparison with Biobrane alone. The EAC do not agree that ReCell plus SSG has demonstrated more rapid healing than SSG alone as this comparison has only been examined in Park et al. (2013) who did not report any healing rate outcomes. ReCell plus dermal grafts have only been studied as case series and no comparative data are available. Further, there was only one study to support the claim that ReCell plus Biobrane provides faster healing or resource savings in comparison to SSG alone. This was a small comparative study with retrospective controls and no statistical testing, but this was reported in three conference abstracts (Rawlins

2011a; Rawlins et al. 2011a; Rawlins et al. 2011b – these three references will be cited as “Rawlins 2011a, etc” for brevity).

The EAC concludes that ReCell may be a clinically suitable alternative to the use of SSGs in mid-deep partial thickness burns. There is no clinical evidence examining the use of ReCell in partial thickness burns which are considered not to require skin grafting (Group A in the Decision Problem). There is also no evidence that demonstrates improved outcomes for the use of ReCell plus SSG in comparison to SSG alone (Group B in the Decision Problem).

Summary of economic evidence submitted by the sponsor

The sponsor’s search for economic studies did not identify any comparative economic publications that included ReCell, but identified papers on general burns care that could be used for resource identification for standard care. The sponsor conducted a survey of expert opinion to supplement the limited published evidence. The sponsor’s de novo model is the primary economic evidence regarding ReCell.

Summary critique of economic evidence submitted by the sponsor

The sponsor did not identify Wood et al. (2012) as a relevant comparative cost analysis of ReCell plus Biobrane and Biobrane alone compared with conventional dressings, although this was included in the clinical evidence. The sponsor did not include NHS Reference Costs (Department of Health 2012), either as a source of inputs for the model or to validate the model.

The model produced by the sponsor was robust and was supplemented by one-way sensitivity analysis and scenarios. The sponsor identified five underlying assumptions in the model, but the EAC described additional structural assumptions that the sponsor had made. The main weakness of the model is that the evidence underpinning the model is very limited.

External Assessment Centre commentary on the robustness of evidence submitted by the sponsor

The clinical evidence is sparse, generally of low quality and characterised by overlapping patient groups and brief descriptions in conference abstracts. The two highest quality studies are in non-UK settings and do not demonstrate improved healing, better scar outcomes or resource savings. Gravante et al. (2007) is a reasonably high quality randomised trial but is limited to small deep partial thickness wounds. They reported a reduction in the negative consequences of surgical intervention between ReCell and SSG (i.e. smaller donor site and post-operative pain) but an increase in operative time for ReCell. Park et al. (2013) report a reduced length of stay (LOS) for ReCell plus SSG in comparison to SSG alone, but the patient populations are not strictly comparable. The evidence cannot be generalised to patient populations outside those in the studies and does not strictly reflect the Decision Problem.

The relative outcomes of the treatment options in the sponsor’s de novo economic model have been shown to be relatively robust using both sensitivity and scenario analysis. However, the drivers for

the cost saving are dependent on clinical benefits and resource savings that are supported by poor evidence and clinical opinion.

Summary of any additional work carried out by the External Assessment Centre

The EAC conducted an additional literature search for clinical evidence that we considered to be broader than that undertaken by the sponsor. The EAC attempted to contact several of the authors for clarification and additional data but obtained only a small amount of information. The EAC has examined the heterogeneity of the patient population, interventions and comparators and attempted to categorise the available evidence accordingly.

The EAC also conducted an additional literature search for economic evidence and conducted quality checks on the economic analysis reported in Wood et al. (2012) and for the sponsor's economic model. The model costs were validated using NHS Reference Costs and data from Wood et al. (2012).

2 Background

2.1 Overview and critique of sponsor's description of clinical context

Current clinical management

The sponsor indicates the variety of treatment strategies in use depending on the individual injury and local burn service preferences. They state that patients with burn injuries are taken to theatre for wound cleaning and assessment within the first two days post injury. At this point superficial dermal burns are treated with debridement and conventional dressings and full thickness burns are debrided and have split thickness skin grafts (SSG) applied. Partial thickness and indeterminate thickness burns are debrided and dressed with either conventional or biosynthetic dressings (Biobrane) with a view to reassessment of the wound at 7-10 days. The sponsor indicates that patients will usually remain as an in-patient with a daily change of dressing (COD) which may be carried out under general anaesthetic (GA). If at the time of reassessment the wound has not healed sufficiently, delayed skin grafting will be used. If injuries are extensive this may take place in stages due to a scarcity of donor sites and the need to allow existing donor sites to heal before re-cropping.

ReCell in the clinical pathway

The sponsor indicates that ReCell could be introduced into this care pathway either at the initial treatment stage or at the delayed grafting stage. They state that the application of ReCell at initial treatment in partial or indeterminate thickness burns may promote better healing and may reduce the extent of later skin grafting. They also state that the dressings are not disturbed until the wound is reassessed at 7-10 days and that patients may be discharged and reassessed as an outpatient.

Additionally, ReCell may be used in conjunction with meshed SSG either initially or at a later stage. The sponsor states that the use of thinner or more widely meshed grafts incurs an increased risk of graft loss but that the addition of ReCell mitigates this increased risk. They suggest that the additional application of ReCell to a thin meshed graft will reduce the persistence of the mesh pattern in the healed skin, reduce the risk of graft failure and therefore allow wider meshing to be used more routinely which will reduce the donor site areas required.

The sponsor states that following acute treatment for burn injuries there is a need for patient education regarding the nature of the wound healing and the potential need for additional dressings or skin grafts to protect wounds from re-injury. The treatment of healed scars is outside the scope of this evaluation and is not considered further.

EAC comments on the clinical pathway

The EAC agree that obviously superficial dermal and full thickness wounds would receive early treatment with conventional dressings and skin grafts respectively. However, expert advisers indicate that Biobrane is in common use in the UK and this is also used in early treatment of more superficial dermal burn injuries, particularly over approximately 5% total burns surface area (TBSA).

Patients with partial thickness or indeterminate burns may be treated with conventional or biosynthetic dressings and then reassessed at 7-10 days. However, the sponsor has not referred to the use of the MoorLDI2 Burn Imager in their submission. Expert advisers indicate that this is a relatively common use in specialist burn services. It is used at around 2-5 days post-injury to aid determination of healing time in indeterminate burns and may enable earlier treatment and reduce the frequency and extent of skin graft operations (NICE 2011). The sponsor indicates that in such cases ReCell would be applied at 0-2 days post-injury.

Expert advisers and published evidence indicates that many patients do not remain as in-patients beyond the first COD post-surgery. Patients may remain as in-patients depending on the size and location of the burn, their level of pain, age of the patient and also practical considerations such as distance from home (Griffiths et al. 2006). Paediatric patients are more likely to require COD in theatre with GA. Following surgery, conventional dressings are usually changed no more frequently than every other day, either in theatre (for larger and more painful burns), on the ward or in outpatient dressing clinics. Alternatively Biobrane remains attached to the wound surface and only requires secondary dressings to be changed for wound inspection, for trimming the detaching dressing or when they are dirty. If ReCell is covered with conventional dressings the primary dressings should remain undisturbed for 5 days (manufacturer's instructions), but the outer dressings may be changed sooner so that the wound can be inspected for infection. Most COD occur every 2-3 days.

The EAC understands that ReCell is used in combination with SSGs, but the impact of this on the current patient pathway is unclear. An expert adviser indicated that burn wounds that have not healed as expected within two weeks may be treated with ReCell, presumably as an alternative to delayed skin grafting. Also, many of the studies included in the clinical evidence involve the use of ReCell (alone or with Biobrane) in mid-deep partial thickness burns in comparison to SSG. Expert advisers have indicated that this could be an appropriate use of the ReCell technology.

Epidemiology

The sponsor has used data from the Hospital Episode Statistics (HSCIC 2012) for England from 2011-2012 and data from the UK burn injury data from the International Burn Injury Database (iBID, NBCG 2008) to estimate the size of the appropriate patient population. Although not precise and prone to ambiguous definitions these are appropriate sources of UK incidence data. The iBID reports are difficult to interpret as data definitions and sources are not provided, however this does suggest that there are around 4000-7600 admissions to specialist burn services in England and Wales each year. A definition of burn severity categories is not provided but 'Minor' and 'Moderate' are identified as suitable for treatment at a Burn Facility, 'Moderate/Severe' and 'Severe' at a Burn Unit and 'Severe' and 'Severe/Complex' at a Burn Centre.

2.2 Overview of sponsor's description of ongoing studies

The sponsor identified a single ongoing study in their submission. This is a multicentre randomised within-patient controlled study investigating the use of ReCell in treating scars from skin grafts (NCT01476826). This US/Canadian study is out of scope as it is not treating the acute burn injury.

The EAC identified a single ongoing trial that is within the scope. This is a multicentre randomised, within-patient controlled feasibility study in the US in collaboration with the Department of Defence and is being conducted for an FDA license for ReCell (NCT01138917). Treatment with ReCell is being compared to split thickness meshed skin graft in second degree burns of at least 100cm² in adults. (Whether the comparator includes unmeshed skin graft is unclear from the information available.) The end date for data collection is July 2013 and the estimated completion date is March 2014 (www.clinicaltrials.gov, website accessed 20/09/13). However in an email the sponsor indicated that this trial has encountered recruitment problems and is not now expected to complete until 2015 at the earliest.

2.3 Critique of sponsor's definition of the decision problem

The sponsor has not altered the Decision Problem from that defined in the final Scope.

Population definition

There are two patient population groups defined in the Decision Problem. The EAC has labelled these as Group A and Group B for ease of reference throughout the Assessment Report:

- partial thickness burns including scalds caused by hot water where mesh grafting is not required (Group A)
- large area burns; full thickness or deep partial thickness burns including where mesh grafting is required (Group B)

The sponsor's search strategy did not distinguish between these, and their assessment of the clinical evidence is not separated into these groups. The EAC has closely examined the patient population definitions in the scope, the sponsor's submission, the available clinical evidence and information provided from clinical experts. We have determined that defining patient populations in burn injuries is a complex issue.

Heterogeneity of patient condition

Firstly, burn injuries are highly individual; their treatment depends on size, location and depth, and a single burn wound may vary in depth and require multiple treatment modalities. There are differences between adults and paediatric patients, as indicated in the referral guidelines.

Definition using referral criteria for specialised burn services

Secondly, both groups are defined as involving patients who are treated in Burns Units or Centres. Specialised services for burns in England and Wales are organised into a three-tiered level of service provision – Facility, Unit and Centre (as recommended in the National Burn Care Review 2001). The full referral guidelines for these are described in the National Burn Care Referral Guidance (National Network for Burn Care 2012). This indicates that the minimum TBSA for the populations considered in the Decision Problem would be 1-5% in paediatric patients and 5-10% in adults (depending on burn depth).

Table 1: UK specialist burn services referral guidelines (NNBC, 2012)

		Facility	Unit	Centre
Paediatric	TBSA	≥ 2% and < 5%	≥ 5% and < 30% ≥ 5% and < 15% (<1 yr)	≥ 30% ≥ 15% (< 1 yr)
	Depth	All full thickness burns	≥ 2% full thickness (< 10 yrs) ≥ 1% full thickness (< 6 mths)	≥ 20% TBSA if full thickness
Adult	TBSA	≥ 3% and < 10%	≥ 10% and < 40%	≥ 40%
	Depth	Any full thickness burns	≥ 5% and < 40% (if no blanching)	

However, amongst the four regional Burn Care Networks in England and Wales, two currently use an interim service designation (NHS Specialised Services 2011) and therefore these services are not fully defined. Also, patients who live locally to a specialist burns services but who have a burn injury severity below the minimum referral criteria would also be treated there. So an adult burn Centre will treat patients with burns from 3% TBSA upwards, but accept patients with very large burns from a wide geographical area. This indicates that defining a patient population by the type of service in which they are treated will not necessarily be consistent. The body surface area of a typical UK adult is approximately 1.7-1.9 m² (Sacco et al. 2010), so that a single ReCell kit covering a wound area of 320 cm² is equivalent to around 1.5-2% TBSA. Therefore an adult treated in a Burn Facility for a 9% TBSA partial thickness burn (for example) would be suitable for treatment with up to 4 or 5 ReCell kits. By strictly following the patient population definition in the Decision Problem this evaluation may exclude appropriate burn injuries that are treated in burn services not designated as Units or Centres.

Definition using burn depth and requirement for meshed grafts

Thirdly, the distinction between the Decision Problem groups is intended to separate less serious and more serious burn wounds. No mention of indeterminate thickness burns is made in the Decision Problem, suggesting that the intention in the scope was that the use of ReCell should be delayed until definitive wound assessment is possible, either following several days wait or using the MoorLDI2 Burns imager (NICE 2011). The groups are partly defined by the requirement for meshed graft. Full thickness burns require skin grafting as the regenerative capacity of the skin has been lost. Deep partial thickness burns, and partial thickness burns that do not heal within around 10-14 days, also require skin grafting to speed up the healing process as long healing times are associated with poor scar outcomes. Both the scope and Briefing Note for this evaluation state that meshed grafts are used only in “extensive wounds” (undefined) suggesting that Group B should be restricted to large area burns. However, information from expert advisers indicates that meshing is commonly applied to all skin grafts except for those used on the face, hands and groin.

Heterogeneity of patient populations in the clinical evidence

Fourthly, in the studies included in the clinical evidence burn injury depth is described and grouped in various ways. For example:

- partial, deep partial and full thickness considered separately (Park et al. 2013),
- deep partial or full thickness burns considered as a group (Sen et al. 2012),
- mid-deep dermal burns considered as a group (Rawlins 2013; Echlin et al. 2012a),
- partial thickness scalds anticipated to benefit from surgery and therefore would not heal within 10 days (Wood et al. 2012),
- scalds and flame burns considered combined (Dunne and Rawlins 2013; Park et al. 2013) or separately (Rawlins et al. 2011a; Wood et al. 2012).

EAC interpretation of the patient population in the Decision Problem

A strict interpretation of the Group A population would include all partial thickness burns and scalds, including those that may require sheet skin grafts. However, the comparator for this group does not include skin grafting, suggesting that this group was not intended to include patients who would require skin grafts (meshed or unmeshed) and therefore restricting this to the more superficial dermal wounds that are expected to heal without skin replacement. This is reinforced by the 'Reasons for developing guidance' in Section 2 of the scope that defines partial thickness as burns where 'only ReCell is used' rather than 'as an adjunct to skin grafting'. The EAC therefore interprets the Group A population as:

partial thickness burns or scalds where skin grafting (meshed or unmeshed) is not required.

The definition of the Group B population is ambiguous and varies between the population, intervention and comparator sections of the Decision Problem. It is unclear whether this represents:

- only large area burns, which are full or deep partial thickness (and may require meshed grafts), or
- all large area burns, and all full or deep partial thickness burns that require meshed grafts, or
- only large area burns, which are full or deep partial thickness and require meshed grafts.

Meshed skin grafting is included in this group as part of the intervention or comparator but not unmeshed grafting. As the scope reserves meshed grafts for use only in extensive wounds this suggests that only larger burns should be included in this group. However, this interpretation would exclude smaller deep partial and full thickness burns from this evaluation of ReCell. (The difference between 'smaller' and 'larger' being defined possibly by the need to mesh grafts at a higher ratio due to a lack of suitable donor sites.) The statements in Section 2 of the scope indicate that the effect of using ReCell in any full or deep partial thickness burn should be included in the evaluation. The EAC therefore interprets the Group B population as:

full thickness or deep partial thickness burns where skin grafting (including meshed grafting in larger burns) is required.

Clinical evidence appropriate to the patient populations

For the reasons described above it is difficult to separate the clinical evidence into the two Decision Problem patient populations. Both the sponsor and the EAC have included all the studies they have identified in which ReCell has been used to treat acute burn wounds; i.e. no clinical evidence was excluded on the basis that it did not exactly match one or other of the patient populations. The EAC has further attempted to classify each study according to its patient population, intervention and comparator. This is shown in Table 10 in section 3.5.

Decision Problem Group A patient population

Wood et al. (2012) compared scalds treated with ReCell plus Biobrane versus Biobrane alone or standard dressings. This is consistent with Group A. However, the patient population was defined as wounds which were “anticipated to benefit from surgery and therefore would not heal within 10 days”. This is more consistent with the Group B population but this study has been retained in Group A as it is the only study that compares ReCell with standard dressings. Rennekampff et al. (2011) and Hiller et al. (2013) described the injuries in their case series as “partial thickness”, and without additional information the EAC has assumed that these also correspond to Group A.

Decision Problem Group B patient population

The remaining studies investigated the use of ReCell in mid or deep partial thickness or full-thickness burns in which surgical intervention (grafting) would (otherwise) be required. In two studies (3 references; Park et al. 2013; Sen et al. 2012 [REDACTED]). ReCell was used in combination with grafting. In the remaining studies ReCell was applied either alone or with Biobrane and where a comparator was used this was meshed or unmeshed skin graft. In these patients with mid to deep partial thickness burn wounds (where a dermal component was still retained) ReCell was being used as an alternative to split thickness skin grafting (SSG). This represents a different intervention in a Group B patient population than that described in the Decision Problem. The EAC considered whether this use of ReCell was appropriate in a UK context. The provenance of several of the conference abstracts is unclear but at least two of these studies were conducted in the UK (Dunne and Rawlins 2012a; Echlin et al. 2012a). An expert adviser also indicated that this was an appropriate treatment. Therefore we assume that this practice is appropriate to the UK.

Adult and paediatric populations

Several of the studies included in the clinical evidence include only adult patients, or only paediatric patients with scald injuries. (Scalds are the most common source of burn injury in children.) Neither the sponsor nor the EAC have separated the evidence into age groups and there was no suggestion in the clinical evidence or the sponsor’s submission of differential outcomes between adults and children treated with ReCell. An expert adviser indicated that paediatric patients may be given general anaesthesia during dressing changes more frequently than adults, but this outcome was not included in any of the clinical evidence studies.

ReCell in hypopigmentation populations

The sponsor also separately collated evidence in a population of patients with hypopigmentation (scars and vitiligo) in order to identify pigmentation outcomes which may not have been included in the acute burn studies. Such patients are outside the scope of this evaluation. Additionally expert advisers did not think that outcomes from these indications could be extrapolated to acute burns wounds. These studies have been excluded by the EAC.

Intervention

The technology in the sponsor's submission matches that in the Scope. ReCell is a stand-alone, battery-operated kit for the processing of a thin split thickness skin biopsy (up to 4 cm²). The device heats a Trypsin solution into which the skin biopsy is placed. After 20-30 minutes the epidermal cells can be scraped off the biopsy and mixed with a buffer solution for application by spraying or dripping onto the wound. The suspension includes a mixed cell population of fibroblasts, keratinocytes, melanocytes and Langerhans cells. These are intended to attach to the wound and proliferate thus accelerating healing.

The device obtained a CE mark in March 2005. ReCell is a Class III medical device and the sponsor has provided the EAC with a copy of their revised Declaration of Conformity dated January 2012. The sponsor has satisfied the regulatory requirements and supplied the EAC with all necessary documentation.

In their submission the sponsor claims that ReCell is in wide use in the NHS, including at least eight specialist burns services.

Comparator(s)

Only one study includes standard or biosynthetic dressings as a comparator as defined in Group A in the Decision Problem (Wood et al. 2012). The sponsor did not provide any additional evidence in the clinical submission. However, in the economic submission they included four questionnaires from burn surgeons regarding their experience of using ReCell in comparison to conventional dressings and Biobrane. Two of these respondents are also NICE MTEP expert advisers.

As described above, unmeshed split thickness skin grafting was not explicitly included in the comparators for Group B. The sponsor and the EAC have included studies where the skin grafts were not meshed, where there was a mixture of meshed and unmeshed grafts and where there was insufficient information to determine whether the graft was meshed.

There is only one study in which ReCell plus split thickness skin grafting is compared to skin grafting alone, although in this study the patient groups are not identical (Park et al. 2013). In another study ReCell is used in a case series in combination with split thickness dermal grafts (Philp et al. 2013; Sen et al. 2012). The expert questionnaires referred to above also included questions regarding the comparison between ReCell plus skin graft versus skin graft alone.

Outcomes

Most of the outcomes listed in the Decision Problem have been addressed by one or more clinical studies included in the sponsor's clinical evidence submission. Additional evidence identified by the EAC supplemented this information. Those outcomes described in the Decision Problem that are not included in the clinical evidence are:

- Re-admission to hospital for management of scarring
- Transfusion rates during skin grafts
- Number of donor sites
- Growth rate in children

Scar outcomes are reported as multidimensional scales (Vancouver scar scale and visual analogue scale), but pigmentation is not reported separately. Scar outcomes were assessed up to 6 months following treatment (where time of assessment is reported) and do not necessarily represent long term responses. The sponsor included a subsidiary literature search for pigmentation outcomes following the treatment of hypopigmented lesions (scars and vitiligo) but these papers were determined to be outside the scope of the evaluation.

Additional outcomes that were reported in the clinical evidence were graft loss or graft take following the initial surgical treatment and the requirement for subsequent skin grafting. Graft loss or take following initial SSG is understood to refer to how much of the graft has integrated to the wound surface. Graft loss or take following treatment with ReCell is understood to refer to the extent of epithelial regrowth over the wound. Subsequent grafting could occur where early treatment (including SSG) has failed to achieve the intended complete wound healing or where early treatment (not including SSG) is intended to reduce the number or extent of skin grafts required at 10-21 days post-injury.

Cost analysis

The sponsor stated that there was insufficient data to model the inputs for the Group B cost analysis and has therefore only provided a cost analysis for Group A. Their de novo model compares the cost of treatment between ReCell (with and without Biobrane) and conventional dressings or Biobrane alone. The burn wound in the base case model was defined as partial thickness with no definite areas of deep involvement and an area of 640cm² (the maximum treatment area for two ReCell kits). In adults this corresponds to approximately 3-4% TBSA and for a 2 year old child this would be approximately 10-12% TBSA. This is appropriate for inclusion in Group A. However, there may be substantial differences in the treatment protocols for an adult with a 4% partial thickness burn and a young child with a 10% partial thickness burn.

Subgroups

No subgroups were identified in the Decision Problem.

Special considerations, including issues related to equality

In the Decision Problem special consideration was given to pigmentation outcomes in patients with darker skin and to the use of porcine-derived trypsin in the ReCell kit.

The sponsor also described improved pigmentation outcomes as a key claimed benefit of ReCell and that its use may result in better colour matching in patients with darker skin. The sponsor conducted a subsidiary literature search to identify studies specifically addressing ReCell use in hypopigmented scars and vitiligo lesions. However the outcomes in this population cannot be extrapolated to the treatment of acute burns and these studies have been excluded from the EAC's analysis. Pigmentation is included in qualitative scar scale assessments in the clinical evidence but is not reported separately. In Gravante et al. (2007) the scar assessment specifically only included pigmentation and vascularity. None of the included studies report skin colour or ethnicity of their patient population or report any difference in outcomes with reference to skin colour. One expert adviser indicated that ReCell appears to produce better pigmentation outcomes than would otherwise have been expected (including in patients with darker skin), but that this was anecdotal.

The sponsor notes that the porcine origin of trypsin is 'well-recognised' and that Biobrane also contains material of porcine origin. They state that advice from clinicians is that patients and their families are comfortable making a decision about the use of both products according to their beliefs. The expert advisers indicated that either all patients are routinely informed about the nature of the product or only patients who may be suspected to object.

No additional equality issues have been identified by the sponsor or the EAC.

3 Clinical evidence

3.1 Critique of the sponsor’s search strategy

The sponsor conducted a single search for both populations from the scope. This is sensible considering the small number of studies likely to be found, the difficulty of categorising burn types and the indexing methods of the databases.

The sponsor searched the four reference databases stipulated in the instructions. Their search strategy was relatively simple, combining terms for burns and scalds with terms to describe ReCell. This latter consisted of ‘ReCell’ as a textword or the combination of ‘autologous’, ‘cell’ and ‘harvest’ within 3 words proximity. In an email the sponsor states that the last three search terms were taken from the description of the technology - “non-cultured autologous cell harvesting” – and that studies using cultured cells were excluded after the search. The sponsor further indicated that no studies were identified solely on the basis of these three combined terms.

The EAC considered this strategy to be somewhat restrictive and redundant. The term ‘harvest’ relates to the detail of the ReCell process and may not appear in an abstract. Also, we considered that ‘autologous’ and ‘harvest’ were unlikely to be found in proximity as only autologous cells are harvested during a surgical procedure. The EAC therefore conducted an additional search using a similar strategy to that of the sponsor, but replacing the combination of ‘autologous’, ‘cell’ and ‘harvest’ with ‘cell’ in combination with ‘spray’ or ‘suspension’ (see Figure 1 for a comparison of search strategies and section 3.9 and Appendix 1 for details of the additional work done). The EAC considered this strategy to be more generic, however all relevant studies identified by the EAC included ‘ReCell’ in the title and/or abstract and therefore these additional search terms were redundant.

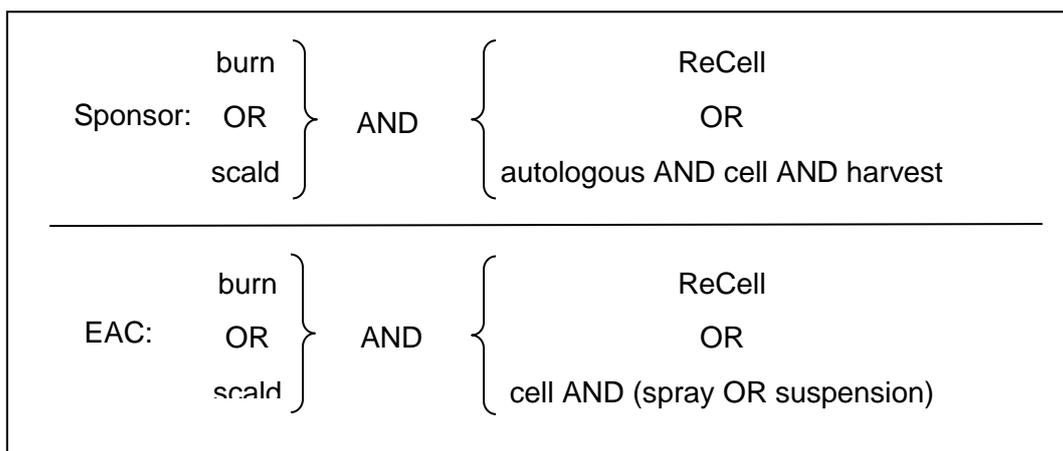


Figure 1: Comparison of sponsor’s & EAC’s database search strategies

The sponsor additionally used a list of known projects. This was not included in the clinical submission but was provided to the EAC on request. They also hand searched the abstracts for four burns-related conferences for the past 5 years: British Burn Association, European Burn Association,

American Burn Association and the International Society for Burn Injuries. The rationale for limiting this search to 5 years was not provided. The EAC additionally identified the Birmingham Burns Association as a suitable conference and searched the available proceedings for the years 2013 and 2010. (These were the only years identified. It is believed that this conference only meets every three years.)

The sponsor's search strategy was effective and reasonably thorough. It is unlikely that suitable studies would be unknown to the sponsor and all studies identified by the EAC have used the brand name in the title or abstract of the reference. Therefore all additional studies identified by the EAC should have been identified by the sponsor.

3.2 Critique of the sponsor's study selection

The inclusion criteria deviated from the scope slightly:

- **Population:** The sponsor defines the indication as 'flame burns and scalds', whereas the Scope does not specify flame burns. This may have excluded other types of burn, e.g. chemical burns.
- **Intervention:** The sponsor defines the intervention as ReCell 'alone or in combination with other treatments', thus combining the two population groups. The Decision Problem restricts the intervention to ReCell plus biosynthetic or standard dressings, and ReCell plus skin mesh graft. This may result in the inclusion of additional types of combined interventions.
- **Comparator:** This was not defined in the selection criteria.
- **Outcomes:** Outcomes are as specified in the Decision Problem with three additions – analgesic/anaesthetic resource, and other resource or patient-relevant outcomes not otherwise specified. The Decision Problem outcomes were not exhaustive so the addition of other outcomes is consistent and appropriate.
- **Study design:** Systematic reviews with quantitative outcomes, controlled trials, observational studies and case studies were included. Narrative reviews without patient effectiveness data, single case reports, animal studies and in vitro studies were excluded. Although single case studies cannot provide comparative data they may contain information on adverse events, so these should have been examined for any data relating to this.
- **Language:** no restrictions were applied. This is appropriate as ReCell originates in Australia and has regulatory approval in multiple non-English speaking countries.
- **Date:** The sponsor's search was limited to studies published from 1995 onwards. This is appropriate as the technology was developed during the 1990's and the ReCell device was launched in 2005.

3.3 Included and excluded studies

According to the PRISMA diagram in Figure 1 of the sponsor's submission 61 records were identified from their literature search of which 50 were excluded:

- 22 were for indications other than thermal burns,
- 13 were not evaluations of ReCell,

- 10 were narrative reviews,
- 3 were basic science/animal studies
- In 2 ReCell use was incidental to the study objectives

A list of excluded studies is not provided. Non-thermal burns (e.g. chemical) are not excluded in the Scope, however the EAC did not identify any relevant studies of ReCell in non-thermal burns. Other criteria for excluding the studies appear to be appropriate (but see below for additional studies included by the EAC). One study (included in the 61 studies above) was initially included but then excluded by the sponsor on the basis of insufficient data (De Angelis B. et al. 2009).

The sponsor therefore included eleven references: 3 peer-reviewed journal papers and 8 conference abstracts. Two of the journal papers were randomised controlled trials (Gravante et al. 2007; Wood et al. 2012) and the third was a retrospective multiple regression study (Park et al. 2013). One journal paper (Park et al. 2013) and 1 conference abstract [REDACTED] were unpublished at the time of submission.

- Gravante et al. (2007) conducted a randomised controlled trial in adult patients with deep partial thickness burns up to 320cm² comparing ReCell alone (n=42) with meshed and unmeshed SSG (n=40).
- Wood et al. (2012) conducted a three-arm randomised controlled pilot study in paediatric patients with partial thickness scalds anticipated to require surgery, comparing ReCell plus Biobrane (n=5), Biobrane only (n=4) and standard care (silver and hydrocolloid dressings, n=4).
- Park et al. (2013) conducted a retrospective analysis of patients with burns requiring surgery over an 8 year period. Multiple regression was used to assess the association between surgical modality and outcomes (infection, graft loss and length of stay). Treatment with ReCell alone (n=73) and ReCell plus SSG (n=264) were compared to SSG (n=387).
- Dunne and Rawlins (2012a) conducted a non-comparative retrospective review of paediatric patients with scalds (n=40). Different levels of burn injury have separate treatments, with ReCell (plus Biobrane) used only in mid-deep dermal burns (n=13).
- Rawlins (2013) conducted a retrospective observational comparative study in paediatric patients with deep dermal scalds treated with ReCell (n=11) or with SSG (15).
- Rawlins et al. (2011a) conducted a mixed method pilot study in adults with deep dermal burns comparing treatment with ReCell plus Biobrane (prospectively recruited, n=5) against matched controls treated with standard SSG (assumed to be retrospective, n=10).
- Echlin et al. (2012a) reported a case series of patients with mid to deep dermal facial burns treated with ReCell (n=5).
- Echlin et al. (2012b) reported a case series of patients with donor site wounds (at risk of delayed healing or requiring recropping) treated with ReCell (n=9).



- Palombo et al. (2012) reported a case series of paediatric patients with scars from scalds treated with ReCell (n=6).
- Sen et al. (2012) reported a case series of adult patients with deep partial or full thickness burns treated with split thickness dermal grafts (STDG)¹ and ReCell (n=5). (Feasibility study for [REDACTED].)
- [REDACTED].

Studies included by the EAC

Nine additional references were identified by the EAC in our literature search (detailed in section 3.9). Three were included in the Briefing Note for this technology (Dunne and Rawlins 2012b; Rawlins et al. 2011b; Sood et al. 2009) and three studies (4 references) were included in the sponsor's list of known studies (Rawlins et al. 2011b; Sood et al. 2009; Dunne & Rawlins 2012b; Rawlins 2011a). Others were identified from database searches or conference listings. All should have been identified by the sponsor's search strategy. The reasons for exclusion are not known although there is some overlap with studies included by the sponsor.

- Sood et al. (2009) conducted an inpatient comparison in patients with partial thickness burns, treating one area with ReCell and another other with SSG (n=10).
- Rawlins (2010) – *abstract unobtainable*.
- Rawlins et al. (2011b) & Rawlins (2011a) conducted a comparison between prospectively recruited patients treated for deep dermal burns treated with ReCell plus Biobrane (n=4) and a matched control group treated with SSG (n=10). (These overlap with Rawlins et al. 2011a.)
- Rawlins (2011b) – *abstract unobtainable*.
- Rennekampff et al. (2011) described a case series of patients with facial burns treated with ReCell (n=5).
- Dunne & Rawlins (2012b) – conducted an observational comparison between paediatric patients with scalds treated with ReCell (n=11) or SSG (n=10). (Overlap with (Rawlins 2013).)
- Dunne and Rawlins (2013) reported a case series of patients with mid-deep dermal burns treated with ReCell plus Biobrane (n=21).
- Hiller et al. (2013) reported a case series of patients with partial thickness facial burns treated with ReCell (n=5). (Possible overlap with (Rennekampff et al. 2011).)

¹ Split thickness dermal grafts consist of recropping an SSG donor site to produce a thin layer of dermal tissue for grafting purposes.



Studies excluded by the EAC

Two conference abstracts identified by the sponsor in their main literature search were excluded by the EAC.

- Echlin et al. (2012b) treated the skin graft donor sites of 9 patients where there was a risk of delayed healing or where donor sites would need to be reused.
- Palombo et al. (2012) treated 6 children with hypertrophic scarring following scalds.

Both studies are out of scope as the intervention and comparator treatments in the Decision Problem are limited to burn wounds.

Table 2: Studies included by the sponsor and the EAC

Study	Patient population	Country	Age	Study design	Time of intervention	Notes	Sample size
Gravante et al. (2007)	Deep partial thickness burns <320 cm ²	Italy	Adult (30-65 years)	Randomised controlled trial	Day 3-5		82
Wood et al. (2012)	Scalds >2% TBSA, expected to require surgery	Australia	Paediatric (8 months – 9 years)	Three-arm randomised controlled pilot study	Day 2	Assessment of early intervention protocol	13
Park et al. (2011)	Burns treated with skin grafting or replacement	Australia	All	Retrospective multivariate analysis	Not reported		722 (770, 48 excluded)
Dunne & Rawlins (2012a)	Scalds of differing depth	UK	Paediatric (9 months-15 years)	Non-comparative retrospective review	Day 1-2		40
Rawlins (2013)	Deep dermal scalds	UK (email from author)	Paediatric	Retrospective comparative observational study	Not reported	Overlap with Dunne and Rawlins (2012b).	26
Rawlins (2011a)	Deep dermal burns	Probably Australia	Adult (17-59 years in the intervention group)	Comparative pilot study using matched controls	Day 2-3	Overlap with Rawlins et al. (2011b) and Rawlins (2011a)	15
Echlin et al. (2012a)	Mid to deep dermal facial burns	UK	All (10 months-50 years)	Case series	Day 9-11 (n=4)	1 patient treated at day 23	5

Study	Patient population	Country	Age	Study design	Time of intervention	Notes	Sample size
Sen et al. (2012)	Deep partial or full thickness burns and donor sites, >50% TBSA	UK, USA, Australia	Adult	Case series	Not reported	Overlap with Philp et al. (2013)	5
Additional studies identified by the EAC							
Sood et al. (2009)	Partial thickness burns	USA	Unreported	Inpatient comparative study	Not reported	Sponsored by Avita but not included in their spreadsheet.	10
<i>Rawlins (2010)</i>	<i>Scald</i>	<i>UK (email from author)</i>	<i>Paediatric</i>	<i>RCT</i>		<i>Abstract unobtainable</i>	
Rawlins et al. (2011b) Rawlins (2011a)	Deep dermal burns to the legs	Australia (email from author)	Adults (17-59 years)	Comparative pilot study with matched controls	Day 2-4 Day 2-3	Overlap with Rawlins et al. (2011a)	14
<i>Rawlins (2011b)</i>	<i>Scalds</i>	<i>UK (email from author)</i>	<i>Paediatric</i>			<i>Abstract unobtainable</i>	
Rennekampff et al. (2011)	Facial burns (assumed to be deep partial thickness)	Germany	Unreported	Case series	Not reported	Overlap with Hiller et al. (2013)?	5

Study	Patient population	Country	Age	Study design	Time of intervention	Notes	Sample size
Dunne & Rawlins (2012b)	Burns	UK (email from author)	Paediatric	Retrospective comparative observational study	Not reported	Overlap with Rawlins (2013).	21
Dunne & Rawlins (2013)	Deep dermal burns	UK (email from author)	All	Non-comparative observational study	Day 2	Retrospective review of cases, overlap with Rawlins (2013), Dunne and Rawlins (2012a,b)	21
Hiller et al. (2013)	Partial thickness facial burns	Germany	Adult (27-81 years)	Case series	Not reported	Overlap with Rennekampff et al. (2011)?	5

3.4 Overview of all included studies

The methodology, critical appraisal and results for each study included by the EAC in the clinical evidence are presented below.

Note that the EAC attempted to contact some authors but was unable to obtain sufficient information to unequivocally define patient overlap between some of the references.

Overview and critique of the sponsor's critical appraisal

The sponsor used the tables provided in the template for their critical appraisal of randomised controlled trials and observational studies. These tables are used for the three journal papers and one conference abstract of a randomised controlled trial (Daniel B et al. 2011 – excluded by the EAC as outside the scope). Other conference abstracts have not been analysed for quality by the sponsor as they are case series and therefore unsuited to critical appraisal. However, Rawlins (2013) and Rawlins et al. (2011a) are comparative studies not case series.

Gravante et al. (2007)

Methodology

The authors conducted a single centre randomised controlled trial in Italy to compare ReCell with skin grafting. Adults (30-65 years) admitted to a burns centre over a 2 year period were eligible if they had deep partial thickness burns of up to 320 cm² that required debridement and epithelial replacement. Exclusion criteria included existing infections, comorbidities or medications that could interfere with wound healing, renal failure and a high anaesthesia risk. Patients were enrolled using a 'sampling chart' to produce homogeneous groups and were treated 3-5 days following the burn. The intervention was ReCell applied to the burn wound and biopsy site. The comparator was split-thickness skin graft meshed to a 1:2 ratio or sheet grafts on the face, hands, feet and genital areas. Follow-up was weekly visits during the first month and then at 3 and 6 months.

Primary outcomes were time to complete epithelialisation and aesthetic and functional quality of the scar. Aesthetic outcomes were assessed using a simplified Vancouver scar scale (pigmentation and vascularity – time not reported) by two plastic surgeons, including one blinded to the procedure. Range of motion was assessed 'with the help of' a physical therapist at 1 and 6 months (blinding not reported). Secondary outcomes were infections, adverse events, medications and post-operative pain (visual analogue score - VAS). The authors also reported procedure time, area harvested and the number of patients requiring a second procedure. Data were tested for normal distribution. Continuous variables were tested using Student's t-test and Mann-Whitney test (for area harvested) and nominal variables using the χ^2 -test and Fisher's exact test.

Critical appraisal

The sponsor correctly identifies the lack of clarity regarding the treatment allocation method. The study is described as randomised and groups were matched for age, gender, burn type and TBSA. No additional information was reported. The EAC attempted to contact the authors for clarification but received no response. The treatment groups are comparable with regards to reported demographic



and burn injury data. Although no age criteria are described in the Methods, in the Results section the authors report that 18 patients were excluded as 'not homogeneous for age' (i.e. below 30 years or above 65 years). The suggestion is that this occurred before treatment allocation, but it is unclear. If patients were removed from the analysis after treatment (e.g. because the 'sampling chart' did not adequately control for age) then this could have biased the results.

The sponsor states that the nature of the treatments made blinding of patients and assessors impossible – the EAC does not consider this to be true for all outcomes. However, several outcomes are unlikely to have been affected by bias (operation time, area harvested, area treated). The sponsor notes that pain could have been affected by bias and the EAC considers that time to complete healing could also have been affected. The accuracy and precision of time to healing is likely to be poor as the patients were described as being assessed at weekly intervals. The sponsor correctly notes that scar assessment was carried out by one blinded and one unblinded assessor and that the blinding status of the physical therapist who assessed functional status was unknown.

Results

A total of 82 patients were treated; 42 in the ReCell group (ReCell only) and 40 in the comparator group (SSG). There were no significant differences in baseline patient characteristics. Follow up was weekly for the first month and then at 3 and 6 months, unless otherwise described. Time to complete epithelialisation was 13 ± 2 days (mean \pm standard deviation) for the ReCell group and 12 ± 2 days for the comparator group (not significant). VSS values were not reported but were not significantly different between the groups. Functional quality of the scar at one month is indicated by the development of contractures. Twelve out of forty-two patients in the ReCell group and 15/40 patients in the comparator group had developed at least one contracture (not significant).

The authors reported no adverse events and no results are given for infections. Post-operative pain was 3.3 ± 1.6 for the ReCell group and 6.8 ± 1.2 for the comparator group (VAS, $p=0.03$). Post-operative analgesia was the same in both groups although patients in the comparator group "complained of an additional painful site (the area of harvesting)". It is not reported whether this information (in the Discussion) was collected as standard or is anecdotal. Procedure time (undefined) was 59 ± 4 minutes for ReCell and 20 ± 6 minutes for the comparator ($p < 0.001$) despite the authors attempt to "optimize operating times" in the ReCell procedure. Donor area harvested was 2.2 ± 1 cm² in the ReCell group and 110 ± 50 cm² in the comparator ($p < 0.001$). Seven out of 42 (17%) patients in the ReCell group and 6/40 (15%) patients in the comparator group required a second procedure to "complete few remaining areas that did not heal". It is unknown whether these procedures were limited to the burn areas included in the study as it is unclear whether patients may have had additional burn areas.

Wood et al. (2012)

Methodology

This is a three-arm randomised controlled pilot study in Australia to compare early surgical interventions with standard care. Paediatric patients presenting or referred to a burn centre over a 12 month period were eligible if they had a scald injury greater than 2% TBSA anticipated not to heal



within 10 days and therefore likely to benefit from surgery. Sample size was intended to be 45 patients. Exclusion criteria included inappropriate initial dressings (not Acticoat and Duoderm), late presentations and unsuitability for general anaesthesia at 48 hours post injury. Clinical assessment of the injury at 48 hours post-injury included laser Doppler scan (moorLDI2), wound measurement (Visitrak) and clinical photographs. Suitable patients were then randomised to equal sized groups using independently prepared sealed envelopes so that the study team were unaware of the next allocation.

The two intervention groups were treated surgically following randomisation. These received debridement and either Biobrane only or ReCell plus Biobrane. The standard care group received continued treatment with silver (Acticoat) and hydrocolloid (Duoderm) dressings on alternate days. The injury was reassessed at 7 or 10 days post injury (inconsistently reported) and patients who were unhealed were treated surgically on day 10. The aim of the study was to investigate early interventions as a means to reduce surgical intervention; primary outcome was therefore surgery at 10 days post injury (yes/no). Additional outcomes were time to healing, pain and analgesia for dressing changes, length of stay, number and duration of dressing changes, complication rates and scar outcomes. Resource use and costs were also reported. Due to small patient numbers only descriptive statistics were used and no statistical tests were used.

Critical appraisal

A very large proportion of the patients screened for eligibility did not meet the inclusion criteria; 112 out of 123 who were excluded did not have burn injuries that were judged to require surgery. The sponsor correctly notes the good randomisation technique but that very small sample numbers resulted in differences in the patient demographics. Of note is the much younger age range in the ReCell plus Biobrane group; patients in this group were under 2 years whereas those in the other groups ranged from approximately 1.5 years to 9 years. The EAC additionally notes that burn area is only reported as TBSA and appears to be slightly reduced in the ReCell plus Biobrane group so the absolute burn area on these patients is likely to be significantly smaller. There was also discrepancy in the reported time of assessment for surgery between the text (10 days) and Figure 1 (7 days).

The sponsor incorrectly states that healing was validated by an independent assessor. An independent clinician was provided with photographs from the recruitment in order to verify the *selection* of patients for inclusion in the trial. As no results of this verification process are reported we assume that the independent clinician agreed with the recruitment choices made by the study team. No blinding of any assessors is reported in this study. The sponsor states that objective outcomes would not be affected by assessor bias, however the EAC does not agree that requirement for surgery is not subject to bias as it is a clinical judgement. The protocol for dressing changes and assessment following the assessment at day 7 or 10 is not described, so the accuracy and precision of the time to healing is unknown. One patient in the ReCell plus Biobrane group was lost to follow-up at 6 weeks. The main author (F Wood) is the co-inventor of ReCell and a director of Avita Medical.



Results

A total of 13 patients were included; 5 in the ReCell plus Biobrane group, 4 in the Biobrane only group and 4 in the standard care (dressings only) group. Data are presented as medians and interquartile range (unless otherwise stated) in the order ReCell plus Biobrane versus Biobrane only and standard care. Patient age was 1.3 (0.8-1.8) years versus 5.5 (1.5-8.8) years and 5.4 (2.5-7.1) years. TBSA was 3.0 (3.0-8.5) versus 6.5 (4.0-13.5) and 4.5 (4.0-5.0).

Surgery at 10 days was 0/5 (0%) versus 1/4 (25%) and 3/4 (75%) patients. Time to complete healing (defined as dressings no longer required) was 16.0 (11.5-18.0) days versus 16.0 (14.25-23.0) days and 36.5 (18.5-47.7) days. Healing assessed by wound measurement at 10 and 21 days was 95% and 100% versus 83.2% and 97.7%, and 71.2% and 90.1%. Slower healing in the standard care group was partially attributed to complications in 2/4 patients in this group. VSS was assessed at 6 months and indicates the score for the worst part of the scar. Scores were 0, 3, 5, 6 versus 2, 3, 3, 9 and 0, 5, 6, 6 (1 patient in the ReCell plus Biobrane group was lost to follow-up before this assessment).

Pain during dressing changes was assessed using three age-appropriate tools; clinician assessment for those under 7 years (CHIPPS for 0-23 months, FLACC for 2-7 years) and the Revised Faces Pain Scale for older children. All these report pain on a scale of 0-10. The pain score at the initial dressing change (pre-randomisation) was compared to the highest pain score following randomisation. The median pain scores were 4.0 to 3.0 (difference of -1.0) versus 4.0 to 2.0 (-2.0) and 4.5 to 5.5 (+1.0). The authors note that the reduction in pain scores in the two intervention groups was potentially related to the longer delay to the first post-randomisation dressing change and therefore more advanced healing. The increase in the pain score for the standard care group may reflect increased anxiety in these children. The number of dressing changes was 5.0 (4.0-6.0) versus 7.0 (5.5-9.5) and 12.5 (8.0-15.0). Fewer dressing changes in the intervention groups were partially attributed to faster healing and fewer changes in the acute phase (Biobrane dressings were not changed between the intervention and reassessment at day 7 or 10).

There were 2 complications in the ReCell plus Biobrane group (wound infection and sepsis), 1 in the Biobrane only group (wound infection) and 2 in the standard care group (overgranulation and graft loss following surgery at day 10). These two patients in the standard care group and another patient in the Biobrane group had poor scar outcome and were treated with steroid injection.

Park et al. (2013)

Methodology

The authors conducted a retrospective multivariate analysis in Australia to determine whether surgical intervention modalities were associated with infection, graft loss and length of stay. All patients admitted to a burn centre who required skin grafting or a skin replacement procedure between January 2004 and December 2011 were eligible. Data were obtained from the hospital's Burns Minimum Dataset linked to laboratory records (iSoft). Exclusion criteria included the presence of burn wound infection or community-acquired infection on admission and positive sputum, urine or blood microbiology culture.



Descriptive statistics, χ^2 two-tailed test and Fisher exact test were used along with univariate and multivariate logistic regression. The outcomes used for the regression models were the presence of burn wound infection (post-operative), graft loss and length of stay. Input variables tested were surgical technique, age category, TBSA, burn depth, inhalational injuries and comorbidity (diabetes – other conditions were too rare). Where the univariate associations were significant at $p < 0.05$ these variables were included in the multivariate analysis. Surgical techniques were SSG, ReCell alone, ReCell plus SSG and CellSpray plus SSG. (CellSpray is a cell suspension produced by the same manufacturer as ReCell, but using laboratory cultured cells). Three patients treated with CellSpray alone were excluded due to low numbers. SSG, alone or in combination with ReCell, was used for burns extending to the deep reticular dermis whereas ReCell alone was used for “deeper” mid-dermal burns.

Critical appraisal

Baseline differences between the surgical intervention groups are not reported. The sponsor states in Table B6a that multiple regression would correct for any differences, however gender and type of burn agent are not included in the model input variables. Also 48 patients out of the initial 770 were excluded, but the demographic and clinical characteristics of these is not reported so that the actual number of patients in each surgical group analysed is unknown. Burn depth is greater in patients treated with SSG than in patients treated with ReCell alone, although burn depth is controlled for in the multiple regression. This retrospective analysis is likely to include those patients in Wood et al. (2012) who received surgical treatment. However, as the methods, aims and outcomes of these studies are very different this overlap is not significant. One of the co-authors (F Wood) is the co-inventor of ReCell and a director of Avita Medical.

Results

Data was analysed for a total of 722 patients. The number of patients in each group is provided before the exclusion of 48 patients and is therefore given as a maximum; ReCell alone $n=73$, ReCell plus SSG $n=264$ and SSG alone $n=387$. Results are presented as odds ratios (OR) and 95% confidence interval with respect to treatment with SSG alone.

The presence of burn wound infection was defined by quantitative swab ($>10^5$ bacteria). Neither ReCell alone nor ReCell plus SSG were associated with burn wound infection: OR 0.78 (0.34-3.42) ($p=0.98$) and 1.23 (0.45-4.52) ($p=0.97$) respectively. Graft loss was defined as greater than around 0.25% TBSA failure or benefiting from “further acute surgical intervention by the Attending Burn Surgeon”. Neither ReCell alone nor ReCell plus SSG were associated with graft loss: OR 0.89 (0.45-2.32) ($p=0.09$) and 1.56 (0.56-3.21) ($p=0.67$). Length of stay (LOS) was not defined, but is assumed to include only the first acute admission. ReCell alone was associated with a significant reduction in length of stay, but ReCell plus SSG was not: OR 0.70 (0.57-0.82) ($p < 0.01$) and 0.98 (0.88-1.10) ($p=0.85$). The authors state that the reduction in hospital stay in ReCell patients should “be interpreted cautiously as the practice indications (wound depth) and timing of surgery...differs markedly from that of SSG”. The authors postulate that the reduction in donor skin harvesting for the ReCell technique may have resulted in lower surgical morbidity and hence reduced LOS.



Dunne and Rawlins (2012a)

Method

The authors review the outcomes for paediatric patients treated according to a new algorithm of early surgical intervention in a UK burn service. Paediatric patients with scalds suitable for early surgical management admitted since January 2011 were included in the data. Wounds were treated 24-48 hours post injury; superficial dermal scalds were treated with Biobrane, mid and deep dermal scalds with ReCell plus Biobrane and full thickness scalds by SSG. The authors briefly report frequency of secondary SSG, hospital stay and scar assessments. Other outcomes are reported in comparison to delayed surgery.

Critical appraisal

The sponsor provides no criticism for case series. This is a non-comparative review of patients with different scald depths treated using different modalities and therefore can be regarded as three independent case series. No information regarding TBSA is provided.

Results

A total of 40 patients were included in the analysis; ReCell plus Biobrane n=13 (mid and deep dermal), Biobrane alone n=20 (superficial dermal) and SSG n=7 (full thickness). Five out of 13 (38%) patients in the ReCell plus Biobrane group, 6/20 (30%) in the Biobrane alone and 2/7 (29%) in the SSG alone groups required subsequent SSG. Mean hospital stay was 4.5 days. The authors report that hospital stay was shorter and scar assessments better in the ReCell plus Biobrane and Biobrane alone groups (values not reported), however these were the less severe burns.

Rawlins (2013), Dunn and Rawlins (2012b)

Methodology

This is a comparative retrospective observational study comparing ReCell and SSG for deep dermal scalds in paediatric patients in a UK burn service. Patients admitted between March 2011 and March 2012 were included if treatment was with ReCell or SSG (according to consultant preference) and patients were followed up for more than four months. TBSA, scar outcomes, operative time and length of physiotherapy follow-up was reported numerically. Five independent clinicians assessed scar quality by viewing images using a visual analogue scale (VAS); 0 (normal skin) to 10 (poor scar). Statistical tests are not reported.

Critical appraisal

The sponsor included this study in their submission but did not provide any critical analysis. TBSA is greater in the ReCell group indicating that the patient populations are different. It is unclear whether the five clinicians were blinded as to treatment allocation.



Dunne and Rawlins (2012b) report data for a subset of the patients in Rawlins (2013). The same number of ReCell patients are reported in both references and all outcomes in this group are identical, with the exception of scar quality. VSS is substantially greater in the earlier paper (4.6 in ReCell and 4.7 in SSG) suggesting an reporting error or a re-evaluation of the images. Information from one of the authors suggests different follow-up periods in the two references. (Further clarification could not be obtained by the EAC.) However, both references indicated that there is no difference in VAS between the two treatment groups, so the outcomes for Rawlins (2013) are presented here.

Results

Rawlins (2013) reports data for 26 paediatric patients; 11 treated with ReCell and 15 with SSG. Mean TBSA was significantly greater in the ReCell group, 6.5% versus 2.9% ($p=0.04$), and mean operative time longer, 87 minutes versus 58 minutes ($p=0.05$). Mean VAS was similar in the two groups, 3.9 (95% CI, 2.8-4.9) versus 3.9 (3.3-4.5) ($p=0.97$). Mean length of physiotherapy follow-up was 21 days in the ReCell group and 40 days in the SSG group ($p=0.29$). Two patients in each group were treated for wound infections.

Rawlins (2011a), Rawlins et al. (2011a) and Rawlins et al. (2011b) (Rawlins 2011a, etc)

Methodology

This is a mixed method comparative pilot study in adult patients with deep dermal flame burns in Australia. Prospective recruitment was used for the intervention group who were treated with ReCell plus Biobrane at 48-72 hours post injury. Comparison was with data from matched controls who received SSG. (This is reported as SSG plus ReCell in Rawlins 2011a). Matching criteria are reported in Rawlins (2011a) as age, burn size and burn location. TBSA and wound healing are reported numerically. Analgesia requirements, and scar assessment at 6 months were reported graphically in Rawlins et al. (2011b). Statistical tests are not reported.

Critical appraisal

The sponsor included Rawlins et al. (2011a) in their clinical evidence submission but did not provide any critical analysis. Rawlins et al. (2011a) reports data for 5 prospectively recruited patients with deep dermal burns. Four of these patients with burns to the legs are reported in Rawlins et al. (2011b) and Rawlins (2011a). It is assumed that the control subjects are selected retrospectively, but this is not reported. There is a suggestion that the ReCell plus Biobrane group may have received earlier surgery than the SSG group. No blinding of assessment was reported and numerical values are only reported for time to healing. Other numerical data have been estimated by the EAC. The difference in time to healing between the two groups appears unusually large and the time to healing quite long in both groups. No information about frequency of wound assessment is reported and the authors have used mean values which may be substantially skewed in small and heterogeneous samples.



Results

Rawlins et al. (2011a) reported data for a total of 15 patients treated with ReCell plus Biobrane (n=5) and SSG (n=10). The mean TBSA in the ReCell plus Biobrane group was 15% (range 9-24%) and mean age was 29 years (range 17-59) – data for the SSG group was not reported (but is matched to the intervention group). Mean time to wound healing (not defined) was 18 days in the ReCell plus Biobrane group and 48 days in the SSG group. The authors state that analgesia at first dressing change and total analgesia requirements were less in the ReCell plus Biobrane group and scar quality using VSS was better (values not reported).

Graphical data from Rawlins et al. (2011b) for a subset of these patients (n=4 and n=10) are estimated as follows. Analgesia requirements for the 24 hour period around the first dressing change were approximately 280 mg Tramadol for ReCell versus 450 mg for SSG. VSS at 6 months was approximately 5.3 for ReCell versus 6.5 for SSG. Length of hospital stay (no data provided) was shorter for ReCell and the authors state that patients returned to work and daily activities faster. Nursing staff commented that ReCell patients were encouraged to mobilise from the day following surgery whereas SSG usually required two days of immobilisation.

Echlin et al. (2012a)

Methodology

This is a case series of patients with mid to deep dermal facial burns treated in a UK burn service. Patients were initially treated with debridement and allograft at 0-2 days. Four patients assessed at 9-11 days post injury and deemed unlikely to heal within 3 weeks from injury underwent debridement and treatment with ReCell and non-adherent dressings. Another patient with late presentation was assessed at 23 days post-injury and was treated with ReCell plus allograft as dressing. The first dressing change was at 3-4 days post surgery. Time to healing was reported numerically. No statistical tests are reported.

Critical appraisal

The sponsor does not provide any critical analysis of case series studies. The authors conclude that ReCell appeared to produce faster healing with reduced skin graft rate and scar formation in this patient population. However, they report no data for their previous standard care (allograft until assessment at 1 week). Very little numerical data is reported.

Results

Data for five patients are reported; 3 scalds and 2 flame burns. Four patients assessed at 9-11 days post injury had a mean time to complete healing of 5 days (maximum 7 days) post surgery. Another patient with late presentation required an additional small SSG to the forehead. The authors state that ReCell “appears to accelerate burn wound healing” and “has decreased the split skin graft rate and subsequent scar formation” in this patient population. The burns service changed their practice to treat such wounds with ReCell if unhealed at 1 week.



Sen et al. (2012), [REDACTED]

Methodology

Sen et al. (2012) [REDACTED] These are two case series of patients, with deep partial or full thickness burns >50% TBSA treated at a UK burn service. Split thickness dermal grafts (STDG) were used when conventional SSG sites were exhausted. The STDG graft and donor sites were treated with ReCell.

[REDACTED]
[REDACTED] Epithelialisation was assessed by 2 independent observers and recorded by photographs in (Sen et al. 2012). Epithelialisation and graft take outcomes are narrative (Sen et al. 2012).

[REDACTED]
[REDACTED].

Critical appraisal

The sponsor does not provide any critical analysis of case series studies.
[REDACTED]
[REDACTED]).

Results

Sen et al. (2012) reported outcomes for 5 patients. Dermal graft take was reported to be complete in all cases. Epithelialisation of graft and donor sites was considered to be comparable to conventional treatment.

[REDACTED]
[REDACTED]
[REDACTED].

Sood et al. (2009)

Methodology

This was an intra-patient comparative study in patients with partial thickness burns in the USA. Two wound areas of 320 cm² were defined; one was treated with ReCell and the other with meshed SSG. Graft take is reported.

Critical appraisal

The authors do not describe the selection of treatment sites or their location (e.g. contiguous or distant). Graft take is reported to one decimal place but the method of measurement is not reported. No other outcomes are reported.



Results

Outcomes for 10 patients are reported. Eight patients had 100% “take” (undefined) in sites treated with ReCell and with SSG. Two patients had reduced take on the ReCell site compared to the SSG site. In one patient (62.4% versus 100%) this was attributed to difficulty with the spray applicator and in the other (73.7% versus 81.5%) it was attributed to the deep partial to full thickness nature of the wound. The authors report a learning curve for use of the applicator and choice of wound.

Rennekampff *et al.* (2011)

Methodology

This is a case series of patients treated with ReCell for facial burns in Germany. It is unclear whether only partial thickness burns were treated (with ReCell) or whether full thickness burns were also treated (using skin grafting or grafting plus ReCell). No other details of patients or treatment were reported. Time to epithelialisation and scar quality were reported.

Critical appraisal

The authors state that “full thickness burns required skin grafting” but it is unclear whether this was part of the initial treatment or later revision. Very little information about methodology or numerical results are reported.

Results

Outcomes for 5 patients were reported. Time to epithelialisation was 7-9 days post surgery. No hypertrophic scars or severe contractions occurred. Skin pigmentation was slightly reduced in comparison to surrounding skin (location of the biopsy was not reported).

Dunne and Rawlins (2013)

Methodology

This is a non-comparative retrospective review of patients treated by the second author. Patients with mid-deep dermal burns suitable for surgical intervention admitted to a UK or Australian burn service between 2009 and 2013 were included. Burns were treated with ReCell and Biobrane at 48 hours post-injury. Narrative outcomes are presented for scar pigmentation and degree of hypertrophy.

Critical appraisal

This review includes 11 children with scalds who may have been included in Dunne and Rawlins (2012b) and Rawlins (2013). A further 8 adults with flame burns may have been included in Rawlins (2011a, etc). No numerical results are reported.



Results

Outcomes were reported for 11 children treated for scalds (mean TBSA 7%) and 10 adults, 8 of whom were treated for flame burns (mean TBSA 9%). The authors report “early wound coverage with good pigmentation and minimal evidence of hypertrophic scarring or donor site morbidity”. One paediatric patient required a later SSG.

Hiller et al. (2013)

Methodology

This is a case series of adult patients with partial thickness facial burns conducted in Germany. Patients were treated with ReCell using a biopsy taken from the retroauricular area and full thickness burns required grafting. Scars were evaluated using the Vancouver scar scale and Cutometer (time not reported). Narrative outcomes are reported, apparently in comparison to the authors previous standard care.

Critical appraisal

This may be the same patient group as reported in Rennekampff et al. (2011), but insufficient information is reported to conclude this. The EAC attempted to contact the authors but received no response.

Results

Outcomes were reported for 5 patients (27-81 years). The authors state an “acceleration in epithelialisation and healing time as well as improvement in scar quality”.

3.5 Results summary

The results from the studies included in section 3.4 are summarised here in Table 3 to Table 9, grouped by outcome and Decision Problem group.

Table 3: Wound healing

Study	Outcome	Measure	Popn. group
Wood et al. (2012)			
ReCell+Biobrane (n=5)	16.0 (11.5 - 18.0)	Time to healing (days) Median (IQR)	A
Biobrane only (n=4)	16.0 (14.25 - 23.0)		
Standard care (n=4)	36.5 (18.5 - 47.7)		
Wood et al. (2012)			
ReCell+Biobrane (n=5)	95.0%	Healing at 10 days	A
Biobrane only (n=4)	83.2%		
Standard care (n=4)	71.2%		



Wood et al. (2012) ReCell+Biobrane (n=5) Biobrane only (n=4) Standard care (n=4)	100.0% 97.7% 90.1%	Healing at 21 days	A
Rennekampff et al. (2011) ReCell (n=5)	7 - 9	Time to healing (days)	A
Hiller et al. (2013) ReCell (n=5)	'acceleration in epithelialisation and healing time'		A
Gravante (2007) ReCell (n=42) Un/meshed SSG (n=40) p	13 ± 2 12 ± 2 NS	Time to healing (days) Mean ± SD	B
Rawlins (2011a, etc) ReCell+Biobrane (n=5) SSG (n=10)	18 48	Time to healing (days) Mean	B
Echlin et al. (2012a) ReCell (n=4)	5, 7	Time to healing (days) Mean, max	B
Philp et al. (2013) ReCell + STDG (n=8)	12	Time to healing (days) Mean	B
Dunne & Rawlins (2013) ReCell + Biobrane (n=21)	'early wound coverage'		B

NS = not significant

Table 4: Scar outcome

Study	Scar outcome	Measure	Pop n. group
Wood et al. (2012) ReCell+Biobrane (n=4) Biobrane only (n=4) Standard care (n=4)	0, 3, 5, 6 2, 3, 3, 9 0, 5, 6, 6	VSS	A
Rennekampff et al. (2011) ReCell (n=5)	'no hypertrophic scars' 'pigmentation slightly reduced'		A
Hiller et al. (2013) ReCell (n=5)	'improvement in scar quality'		A



Gravante (2007) ReCell (n=42) SSG (n=40) p	Not reported Not reported NS	Simplified VSS	B
Gravante (2007) ReCell (n=42) SSG (n=40) p	12/42 15/40 NS	Contractur es	B
Rawlins et al. (2011b) ReCell (n=4) SSG (n=10)	5.3 6.5	Approx. VSS	B
Echlin et al. (2012a) ReCell (n=5)	'decreased...scar formation'		B
[REDACTED]	[REDACTED]		[REDACTED]
Dunne & Rawlins (2013) ReCell + Biobrane (n=21)	'good pigmentation' 'minimal evidence of hypertrophic scarring'		B

Table 5: Subsequent graft and initial graft take/loss

Study	Outcome	Measure	Popn. group
Wood et al. (2012) ReCell+Biobrane (n=5) Biobrane only (n=4) Standard care (n=4)	0/5 (0%) 1/4 (25%) 3/4 (75%)	Surgery at 10 days	A
Dunne & Rawlins (2012a) ReCell+Biobrane (n=13) Biobrane alone (n=20) SSG alone (n=7)	5/13 (38%) 6/20 (30%) 2/7 (29%)	Subsequent SSG	B
Dunne & Rawlins (2013) ReCell + Biobrane (n=21)	1/21 (5%)	Subsequent SSG	B
Echlin et al. (2012a) ReCell (n=5)	'decreased the split skin graft rate'		B
Park et al. (2013) ReCell alone (n=73) p ReCell+SSG (n=264) p	0.89 (0.45-2.32) 0.09 1.56 (0.56-3.21) 0.67	Graft loss Odds ratio (CI) vs. SSG alone (n=387)	B
Sood et al. (2009) ReCell (n=10) SSG (n=10)	93.6% 98.2%	Graft take	B
Sood et al. (2009)			



ReCell (n=10)	8/10 (80%)	100% graft take	B
SSG (n=10)	9/10 (90%)		

Table 6: Pain and analgesia

Study	Outcome	Measure	Popn. group
Wood et al. (2012) ReCell+Biobrane (n=5) Biobrane only (n=4) Standard care (n=4)	4.0 to 3.0 (-1.0) 4.0 to 2.0 (-2.0) 4.5 to 5.0 (+1.0)	Pre/post intervention pain at dressing change Median VAS	A
Gravante (2007) ReCell (n=42) Un/meshed SSG (n=40) p	3.3 ± 1.6 6.8 ± 1.2 0.03	Pain, VAS Mean ± SD	B
Gravante (2007) ReCell (n=42) Un/meshed SSG (n=40) p	No difference in analgesia, but SSG group has 'additional painful site'	Analgesia	B
Rawlins et al. (2011b) ReCell+Biobrane(n=4) SSG alone (n=10)	280 450	Analgesia (mg Tramadol) around 1 st dressing change	B

Table 7: Resource use

Study	Outcome	Measure	Popn. group
Wood et al. (2012) ReCell+Biobrane (n=5) Biobrane only (n=4) Standard care (n=4)	5.0 (4.0-6.0) 7.0 (5.5-9.5) 12.5 (8.0-15.0)	Number of dressing changes Median (IQR)	A
Gravante (2007) ReCell (n=42) Un/meshed SSG (n=40) p	59 ± 4 20 ± 6 <0.001	Procedure time (mins) Mean ± SD	B
Rawlins (2013, etc) ReCell (n=11) SSG (n=15) p	87 58 0.05	Operative time (mins) Mean	B
Park et al. (2013) ReCell alone (n=73) p ReCell+SSG (n=264) p	0.70 (0.57-0.82) <0.01 0.98 (0.88-1.10) 0.85	Length of stay Odds ratio (CI) vs. SSG alone (n=387)	B



Rawlins et al. (2011b) ReCell + Biobrane (n=4) SSG (n=10)	'was shorter in the ReCell and Biobrane group'	Length of stay	B
Rawlins (2013) ReCell (n=11) SSG (n=15) p	21 40 0.29	Length of physiotherapy follow-up (days) Mean	B



Table 8: Wound infection

Study	Outcome	Measure	Popn. group
Wood et al. (2012) ReCell+Biobrane (n=5) Biobrane only (n=4) Standard care (n=4)	1 + 1 /5 1/4 0/4	Wound infection or sepsis	A
Gravante (2007) ReCell (n=42) Un/meshed SSG (n=40)	0/42 0/42	Infection rate	B
Park et al. (2013) ReCell alone (n=73) p ReCell+SSG (n=264) p	0.78 (0.34-3.42) 0.98 1.23 (0.45-4.52) 0.97	Wound infection Odds ratio (CI) vs. SSG alone (n=387)	B
Park et al. (2013) All patients (n=770)	67/770 (8.7%)	Infection rate	B
Rawlins (2013) ReCell (n=11) SSG (n=15)	2/11 (18%) 2/15 (13%)	Infection rate	B

Table 9: Donor site area

Study	Outcome	Measure	Popn. group
Gravante (2007) ReCell (n=42) Un/meshed SSG (n=40) p	2.2 ± 1.0 110 ± 50 <0.001	Area harvested (cm ²)	B

Relevance of the clinical evidence to the scope

The two Decision Problem groups interpreted by the EAC (section 2.3) are:

	Population	Intervention	Comparator
Group A:	Partial thickness burns or scalds where skin grafting (meshed or unmeshed) is not required	ReCell alone, or in combination with biosynthetic or standard dressings	Biosynthetic dressings OR standard dressings
Group B:	Full thickness or deep partial thickness burns where skin grafting (including meshed grafting in larger burns) is required	Skin mesh graft in combination with ReCell	Skin mesh graft alone OR skin mesh graft plus biosynthetic dressing

The papers are shown according to their Decision Problem Group compatibility in Table 10. (See also Section 2.3.)



Table 10: Clinical evidence studies arranged by patient population, intervention and comparator

Study	Country	Patient population		Intervention		Comparator	
Wood et al. (2012)	Australia	Part. thickness scald	A	ReCell+ Biobrane	A	Std. dressing Biobrane	A A
		Part. thickness scald	A				
		Part. thickness scald	A				
Rennekampff et al. (2011)	Germany	Burns	A	ReCell	A	NA	
Hiller et al. (2013)	Germany	Burns	A	ReCell	A	NA	
Park (2013)	Australia	Deep reticular dermal burns	B	ReCell + un/meshed SSG	B	Un/meshed SSG	B
Sen (2012)	UK, USA, Australia	Deep partial or full thickness burns	B	ReCell+STDG	B	NA	
██████████	██████████	██████████	█	██████████	█	█	
Gravante (2007)	Italy	Deep partial thickness	B	ReCell	A	Un/meshed SSG	B
Park (2013)	Australia	Deeper mid-dermal burns	B	ReCell	A	Un/meshed SSG	B
Dunne & Rawlins (2012a)	UK	Mid-deep dermal scalds	B	ReCell + Biobrane	A		
Rawlins (2013), Dunne & Rawlins (2012b)	UK	Deep dermal scalds	B	ReCell	A	SSG	B
Dunne & Rawlins (2013)	UK	Mid-deep dermal burns	B	ReCell + Biobrane	A	NA	
Rawlins et al. (2011a); Rawlins et al. (2011b); Rawlins (2011a)	Australia	Deep dermal burns	B	ReCell + Biobrane	A	SSG	B
Echlin (2012a)	UK	Mid-deep dermal burns	B	ReCell	A	NA	

Sood et al. (2009)	UK	Partial thickness burns	B	ReCell	A	Meshed SSG	B
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Subsidiary literature search for skin pigmentation outcomes

The sponsor conducted an additional literature search specifically to identify studies that evaluated the effect of ReCell on skin pigmentation. They widened the patient population to include all patients with hypopigmentation or vitiligo and combined this with the same search terms to represent ReCell as used in the main search. The sponsors acknowledge that these studies are out of scope, but indicate that they believe the outcomes are relevant for patients with burn injuries. Several of the included studies assess scar quality outcomes using numerical scales (Gravante et al. 2007; Rawlins 2011b; Rawlins 2013; Wood et al. 2012) but pigmentation is not reported separately.

Information from the expert advisers indicated that outcomes from repigmentation treatments for scars and vitiligo was not generalisable to the patients population defined in the Decision Problem.

3.6 Description of the adverse events reported by the sponsor

The sponsor states that no adverse events have been reported by them. The EAC conducted a search of the MAUDE database and did not identify any adverse events related to ReCell.

The sponsor collated adverse events reported in the studies included in their submission. These were limited to typical negative outcomes of burn injuries and are not related to the use of the ReCell device itself. Wound infections, graft loss, additional graft procedures and contractures are reported in several studies and have been included as outcomes in the Results section of this Assessment Report. There is no evidence of any differences in the rates of these events between patients treated with ReCell and other surgical modalities. However, Sood et al. (2011) conducted an inpatient comparison between ReCell and SSG and ascribed a reduced graft take on the ReCell site in one patient (62.4% versus 100%) to difficulty with the spray application of cells. The authors noted a learning curve with respect to choosing appropriate wounds and with the use of the spray applicator.

The device is battery-operated and has a self-test function to be used before being operated. Information on training requirements were not provided. The sponsor indicates that sensitivity to trypsin or sodium lactate could result in an adverse response. However, this is listed in the contraindications on the device instructions and expert advisers indicated that such sensitivity is unlikely as the trypsin is rinsed off the cells before application and sodium lactate is in common use in other applications.

3.7 Description and critique of evidence synthesis and meta-analysis carried out by the sponsor

The sponsor did not carry out a meta-analysis or evidence synthesis due to the heterogeneity of patient populations, interventions and methodologies in the included studies. This is considered

appropriate. The sponsor provided a narrative summary of each study included in their submission although with little critical appraisal.

3.8 Additional work carried out by the External Assessment Centre in relation to clinical evidence

The EAC conducted an additional literature search for studies including ReCell (detailed in Appendix 1, see also Section 3.1). Briefly, the terms 'spray' OR 'suspension' AND 'cell' were used as alternative search terms for 'ReCell'. The following databases were searched: Medline, Medline in process, Embase, Scopus, Web of Science and Cochrane Library. Google Scholar, the Health Management Information Consortium and the York CRD database were also searched using simpler strategies. The journal websites for 'Burns' and 'Burn Care and Research' were searched for articles including the term 'ReCell'. Proceedings for the four conferences identified by the sponsor plus the Birmingham Burns Congress were searched if they were available online. The EAC also checked the sponsor's database of known studies and recreated the sponsor's search strategy as closely as possible.

The EAC's search strategy identified an additional 9 conference abstracts not included in the sponsor's submission. Five of these were determined to be multiple reports of data that was the same or overlapped with references identified by the sponsor.

- Rawlins (2010) may report early results from Wood et al. (2012) – abstract unavailable.
- Rawlins et al. (2011b) and Rawlins (2011a) reported a subset of data from Rawlins et al. (2011a)
- Rawlins (2011b) may report early results from Dunne and Rawlins (2012a) – abstract unavailable.
- Dunne & Rawlins (2012b) was summarised in the ReCell Briefing Note and reports early data from Rawlins (2013).

There were 4 references that provided new or additional information not included in the sponsor's selection.

- Sood et al. (2009)
- Rennekampff et al. (2011)
- Dunne & Rawlins (2013) – may include some patient data from other Rawlins papers.
- Hiller et al. (2013) – possibly the same study as Rennekampff et al. (2011).

All these additional references should have been identified by the sponsor's search strategy. The reasons for excluding these papers is not known. The data from these references have been included in Sections 3.4-3.6.



For the economic evidence submission the sponsor obtained questionnaire data from 4 clinical experts regarding their use of ReCell. Two of these were also NICE MTEP expert advisers, another was a clinician who had experience of using ReCell in the UK and the fourth was the co-inventor of ReCell. The EAC has summarised the relevant clinical information here to supplement the evidence from the clinical studies.

3.9 Conclusions on the clinical evidence

The evidence from all studies included by the EAC is summarised here according to the population groups defined in the scope and in section 2.3. No conclusions can be drawn on four outcomes in the Decision Problem for which no studies provided data: re-admission to hospital for management of scarring; transfusion rates during skin grafts; number of donor sites, growth rate in children.

Decision Problem Group A population and intervention

Only Wood et al. (2012) conducted a study that compares a Group A intervention (ReCell plus Biobrane) with a Group A comparator (standard or biosynthetic dressings). Although this was an RCT the number of patients in each group were too small to allow robust conclusions to be drawn. However the results suggest that ReCell may reduce healing time and may reduce the number of patients that require subsequent grafting in comparison to both other treatment options. Although this study has been included in the patient population for Group A the patients were described as “anticipated to benefit from surgery and therefore would not heal within 10 days”. In other studies this patient population may have been treated with early surgical intervention using either ReCell or SSG. It may also be appropriate therefore to consider this study as using a Group A intervention in a Group B population. However, this is the only study identified that compared ReCell with standard dressings so the results are kept separate.

Decision Problem Group A intervention in Group B population

Most of the studies included by the EAC used either ReCell alone or in combination with Biobrane in a population of patients with mid-deep dermal burns that would otherwise have required additional epithelial cover (e.g. SSG). There are five studies (8 references) in which this treatment is compared with meshed or unmeshed SSG (Gravante et al. 2007; Park et al. 2013; Rawlins 2013; Rawlins 2011a, etc; Sood et al. 2009). Healing times for ReCell alone were not different to SSG in Gravante et al. (2007), but in Rawlins et al. (2011a, etc) they were reduced in the ReCell plus Biobrane group (48 versus 18 days, no statistical test). Scar assessments, infection rates and rates of graft loss/take were similar between the two treatment options. Pain and analgesia requirements tended to be reduced in the intervention group, potentially related to the smaller donor site. Length of stay may be reduced (Park et al. 2013; Rawlins 2011a, etc). Operative time is increased by around 30 mins when using ReCell in comparison to SSG only (Gravante et al. 2007; Rawlins 2013).

Three other studies do not provide comparative data. Echlin et al. (2012a) state that ReCell “appears to accelerate wound healing” (complete healing was achieved in 7 days or less) and has “decreased the split skin graft rate” compared to their previous practice of using SSG. Dunne and Rawlins (2013) state that ReCell “was effective at early wound coverage with good pigmentation and minimal

evidence of hypertrophic scarring” (note that the intervention was ReCell plus Biobrane). Dunne and Rawlins (2012a) state that scar assessments were “good to excellent” in patients treated with ReCell plus Biobrane.

Group B intervention in Group B population

Only 2 studies (3 references) used ReCell in combination with either SSG or STDG. Park et al. (2013) reported that infection rates, graft loss and length of stay were similar to SSG. Author statements in Sen et al. (2012) [REDACTED] indicate that healing time and scar outcomes are comparable to conventional grafting. [REDACTED] is similar to that reported in Gravante et al. (2007) for SSG alone.

Completeness of the sponsor’s submission

The sponsor did not include 9 relevant references identified by the EAC (as described above). However these additional references are all conference abstracts and do not add significantly to the comparative data provided. The EAC does not believe that there was a selection bias by the sponsor. Studies in indications other than acute burn injuries have been excluded from the EAC’s evaluation as these are outside the scope.

The sponsor has commented on the relevance of the evidence to the scope. However they have considered the patient populations, interventions and comparators separately and indicated that each is covered adequately by the submitted evidence. That is, both patient populations, both indicators and both comparators have been covered by some part of the clinical evidence submitted. The EAC has commented on the difference between the groups defined in the scope and those reported in the included studies in sections 2.3 and section 3.6 and summarised the included studies according to the groups (above). This demonstrates that the pre-defined combinations of patient population, interventions and comparators have not been covered by the available clinical evidence.

Sponsor’s interpretation of the clinical evidence

The sponsor’s broad interpretation of the clinical evidence is that ReCell produces outcomes comparable to SSG. However, the sponsor’s statement that adding ReCell to grafts allows more rapid epithelialisation than with SSG alone (section 7.9.1) is not supported by the evidence. Only one study compared ReCell plus SSG with SSG alone and this did not report healing rates (Park et al. 2013). Sen et al. (2012) [REDACTED] reported the use of ReCell plus STDG, i.e. recropping of the same donor site in the same operation. The use of this technique would allow greater wound coverage at one time and may thus enable total patient healing time to be reduced.

The sponsor’s statement that ReCell plus Biobrane is associated with more rapid healing, lower costs and shorter length of hospital stay than with SSG is based on a single study of 5+10 patients (Rawlins 2011a, etc).

The EAC concurs with the sponsor that use of ReCell is at least as effective as standard care (standard or biosynthetic dressings or SSG alone). Differences in outcomes that are a necessary



requirement of the use of ReCell are not in doubt; for example, donor site area and therefore the pain associated with these are expected to be reduced in comparison to SSG alone. Following the application of ReCell the wound should be undisturbed for at least 5 days (manufacturer's instructions) whereas standard dressings are normally changed every other day (Wood et al. 2012; expert adviser opinion). However, the use of ReCell is associated with an increase in operative time. There was no evidence that the addition of ReCell to Biobrane confers any clinical benefits and there was no data comparing the use of ReCell alone with the use of Biobrane alone.

4 Economic evidence

4.1 Published economic evidence

Critique of the sponsor’s search strategy

The sponsor searched three databases; Medline (including in-process), Embase and one specialist health economic database, NHS EED. Other economic databases were not included in the search, for example Econlit.

The strategy used to search for clinical evidence in Medline and Embase, was sufficient to have identified any economic or cost studies on ReCell within these databases. The search strategy for economic evidence in these two databases was extended by the sponsor to include any intervention. The studies identified were comparative cost analyses of dressings or general assessments of the cost of burns care and therefore do not address the questions in the scope. The NHS EED database includes economic studies identified by an extensive weekly literature search. None of the studies identified by the sponsor’s search of NHS EED concerned the use of ReCell.

The	sponsor	included

Critique of the sponsors study selection

The sponsor’s selection criteria were broader than those of the Decision Problem in the scope, such that the intervention was not limited to ReCell or biosynthetic dressings. The rationale for the broader search strategy seems to have been to identify resources for the de novo model. None of the selected studies include ReCell, but either comparative studies of dressings or general assessments of the cost of burns care.

Included and excluded studies

The sponsor included 8 published studies and one unpublished audit, listed in Table C2 of the sponsor’s submission.

Wood et al. (2012) contains data on the cost of treatment with ReCell in an Australia burn service. It was included in the sponsor’s clinical evidence but not the economic evidence, although it is referenced several times in the economic submission. Since there were no other published comparative studies including cost analysis identified, the EAC considers it should be included. It is not clear why the study was excluded by the sponsor.



The EAC excluded all of the sponsor’s selected studies as being outside the scope, since they do not include ReCell. The EAC recognises that some of these studies include relevant sources providing resource data for standard care for the de novo cost model.

Overview of methodologies of all included economic studies

Sponsor included economic studies

- Carayanni et al. (2011) is a comparative cost-effectiveness analysis of oil-based versus povidine iodine-based dressings in Greece.
- Caruso et al. (2006) is a cost effectiveness analysis alongside an RCT of two types of dressing, aquacel and silver sulfadazine based in the USA.
- Fong et al. (2005) is an audit from Australia reporting costs of care for patients receiving two different dressings; acticoat and silvazine.
- Silverstein et al. (2011) is a US RCT comparing two dressings, silver-containing soft foam dressing and silver sulfadiazine cream that includes cost data.
- Pellatt et al. (2010) is a UK (Bristol) assessment of cost of standard care for major paediatric burns.
- Hemington-Gorse et al. (2009) is a UK (Swansea) assessment of cost of standard care for major burns and comparison with HRG costs.
- Griffiths (2006) is a UK (Bristol) assessment of the cost of standard care for 3 paediatric scalds.
- Ahn and Maitz (2012) is an Australian assessment of costs of standard care for 20 adult burns patients.

- [REDACTED]

EAC included economic study

Wood et al. (2012) includes a resource analysis alongside a three-arm RCT conducted in Australia. Paediatric patients with scald injuries were randomised to receive either Biobrane (n=4), or Biobrane plus ReCell (n=5) or standard care (n=4).

Overview and critique of the sponsor’s critical appraisal for each study

The sponsor has applied the quality checklist provided in Table C3 of the sponsor submission template to each of their selected studies, except [REDACTED]



The EAC has completed the quality checklist for Wood et al. (2012) (Appendix 2). The limitations of the Wood study are that it was conducted in Australia and may not reflect UK practice, the very small number of patients included (n=13), the heterogeneous patient population and the limited details of the resources, unit costs and total costs. The range of total costs was very large in each arm and the number of patients very small so it would be unwise to generalise the results.

Does the sponsor’s review of economic evidence draw conclusions from the data available?

From the review of economic evidence the sponsor concludes that there are no published economic studies that answer the questions in the scope, therefore a de novo analysis is required and this is appropriate.

Wood et al. (2012) report the mean costs per treatment arm of the study. These were lowest for the standard treatment arm (Table 11, medians calculated by the EAC).

Table 11: Cost results from Wood et al. (2012) – Aust\$

	ReCell plus Biobrane	Biobrane	Standard dressings
Mean	11337	22733	9431
Median	11745	26174	6751

The authors conclude that the number of bed hours occupied by the patient was the primary driver in determining the overall costs. As this resource use was significantly affected by non-clinical considerations (e.g. distance from home) overall costs do not reflect the treatment modality. The EAC considers the economic evidence from Wood et al. (2012) to be of limited value. Other papers selected by the sponsor include some relevant resource data but do not address the questions in the scope. The main economic evidence to consider is from the de novo model.

4.2 De novo cost analysis

Include a description and critique of the key assumptions related to the model structure.

An executable model was provided in TreeAge format. It is written from the perspective of the NHS. The model was supplied with the inputs set at the base case values. In order to check the results from sensitivity analysis the EAC changed each of the inputs in turn to correspond with those given in the ‘Range’ column of Table C5 in the sponsor submission, re-ran the model and saved the results.

Patients

The patients included in the de novo model are limited to Group A in the Decision Problem. In section 9.1.2 of the sponsor’s submission the patient population is defined as “patients of any age presenting for acute care of partial thickness burns or scalds, where there is no immediate need for mesh grafting”. In section 9.1.5 the indication is described as “partial thickness with no definite areas of deep involvement” – this is consistent with the first description. However the sponsor has used questionnaire data from four clinical advisers to provide data for their model. In their instructions to



these advisers the sponsor describes a “5-10% partial thickness burn of indeterminate depth”. This indicates a burn injury that may require skin grafting and is inconsistent with the other descriptions of the patient population given in the sponsor’s economic submission. Also, in section 9.2.1 the sponsor describes the probability of requiring skin grafting as being dependent on evidence of areas of full thickness burn at 10-12 days. This again indicates a difference between the burn injury actually being modelled and that described in the patient population as consistent with Group A.

The sponsor also uses data from four clinical trials of conventional topical treatments to provide data for the time to healing and proportion of wounds progressing to delayed skin grafting when treated with standard dressings (Caruso et al. 2006; Cuttle et al. 2007; Ostlie et al. 2012; Silverstein et al. 2011). However, these studies have a heterogeneous patient population including partial thickness burns, burns of mixed depth and full thickness burns whereas burn injuries that are consistent with the Group A patient population are (by definition) unlikely to require delayed grafting.

No modelling was conducted for the Group B patient population as the sponsor states that there is insufficient evidence to provide input parameters.

Technology

There are two treatment interventions in the model that include ReCell in accordance with Group A in the Decision Problem; ReCell with biosynthetic dressing (Biobrane) and ReCell with conventional dressings.

Comparator(s)

There are two comparators in the model in accordance with Group A in the Decision Problem; biosynthetic dressings (Biobrane) and standard dressings.

Model structure

The model structure chosen is a decision tree with four primary branches corresponding to the two interventions and two comparators under consideration. Figure 6 in the sponsor submission shows only part of the model structure. The full structure is shown in Appendix 3 of this report. It is reasonable to use a simple decision tree approach in this model because of the limited data available to populate the model. The EAC considers the basic structure to be appropriate.

Assumptions - overt

The sponsor lists five assumptions.

1. The first assumption is that the burn is considered to be partial thickness at the start of treatment, in keeping with the scope (but see Population section above).
2. The second assumption is that the burn requiring treatment is 640cm^2 . The EAC has calculated this as around 3.5% TBSA for a UK adult (Sacco et al. 2010) or up to 10-15% TBSA



for a small child or baby (Sharkey et al. 2001). The sponsor states this corresponded to approximately 5-10% TBSA, depending on the size of the patient. This size of wound is justified by the sponsor as large enough to warrant treatment in a specialist burns service. Also they state that costs for burns care decrease rapidly below 5% TBSA. However, the EAC considers that the two references cited by the sponsor (Wood et al. 2012; [REDACTED]) do not provide evidence to support this conclusion. The EAC considers this an appropriate burn size for Group A in the Decision Problem.

3. The pathway of care is as described in the submission of clinical evidence in section 3.3 of the sponsor submission. All burns are assumed by the sponsor to require initial debridement in theatre. Patients receiving conventional or Biobrane dressings require 20 minutes of theatre time and those being treated with ReCell require 30 minutes. This was based on feedback from the sponsor's clinical advisers but appears to rely on a single response. Two clinical studies demonstrate that the application of ReCell alone requires a mean of 29 minutes additional procedure time compared to SSG alone (Gravante et al. 2007; Rawlins 2013). Although these studies use a different comparator the EAC suggests that the extra procedure time may have been underestimated by the sponsor, particularly for surgeons unfamiliar with the technology. Sood et al. (2009) indicate a learning curve associated with successful use of the ReCell device.
4. Patients are assumed to be treated as in-patients until day 2 when a proportion are discharged and receive dressing changes as outpatients. This assumption is appropriate based upon the sponsor's survey of expert opinion and the EAC communications with clinical advisers.
5. The final assumption is that patients are managed either on a general burns ward or as outpatients.

The sponsor excludes treatment in ITU on the grounds that its high cost obscures other treatment cost differences. If treatment in ITU strongly drives cost as suggested, it should be included in the model unless the sponsor is confident that treatment in ITU is the same in all of the interventions. For this Group A population with 640cm² partial thickness burns it may be appropriate to exclude this because few such patients are likely to require care in ITU [REDACTED]. However the reason given in the sponsor submission for excluding ITU costs is invalid.

Assumptions - hidden

The EAC has identified the following additional underlying assumptions used by the sponsor:

- In-patients are assumed to remain in the burns ward until complete re-epithelialisation. One expert adviser indicated that patients will be discharged unless the size or site of the burn or the level of pain contraindicates this. As patients may be referred from a large geographical area distance from home may also contribute to the decision to remain an in-patient (Griffiths et al. 2006; Wood et al. 2012).



- The sponsor assumes that a greater proportion of patients with conventional dressings are treated as in-patients compared with patients receiving ReCell alone, ReCell plus Biobrane and Biobrane. The EAC has not found supporting evidence for this. Two of the sponsor's clinical advisers suggest that patients in all four treatment arms of the model may be discharged after the first COD on day 2-3 post intervention. A third states that for a 10% burn patients with Biobrane or Biobrane plus ReCell may be discharged at 2-4 days post treatment, patients with ReCell alone at 5-10 days and patients with conventional dressings at 7-14 days.
- It is assumed that the decision to progress to an SSG is made after ten days for all treatments. This is consistent with published clinical evidence although the actual time point for this decision may vary from 7-14 days.
- It is assumed that patients initially treated with Biobrane alone or ReCell plus Biobrane who progress to SSG will then continue with Biobrane dressings after grafting. Three of the clinical experts consulted by the sponsor noted that it is not usual practice to use Biobrane over an SSG.
- It is assumed that complication rates are the same for all interventions, since this is not included in the model. The EAC considers this to be a reasonable assumption based on the clinical evidence for more severe burns.
- The sponsor calculates the *percentage* reduction in healing times for ReCell plus Biobrane and Biobrane compared with standard dressings from Wood et al. (2012) as 23%-62%. They also use intra-patient comparisons from Echlin et al. (2012b) in which 2 patients had graft donor sites treated with ReCell compared to conventional dressings. In this case they calculate a 35% and 80% reduction in healing time. The sponsor also quotes one of their clinical advisers as stating that they achieved a 25-50% reduction in healing time with ReCell. However, the EAC has concluded that the adviser actually described a 25-50% reduction in the need for delayed SSG following treatment with ReCell. None of the four clinical advisers provide information regarding healing time. The sponsor applies a percentage reduction to the healing time for conventional care to calculate values for ReCell alone, ReCell plus Biobrane and Biobrane. The EAC considers that it is reasonable to cautiously apply this reduction to ReCell plus Biobrane and Biobrane alone, but there is no evidence for this in ReCell, since Wood et al. (2012) does not include a ReCell alone treatment group.

The EAC completed a quality check on the sponsor model and submission and found the economic submission to be of acceptable quality and well reported.

Clinical parameters and variables

The time horizon used in the model is intended to be the period of the acute episode of care and is chosen to be 21 days. This is appropriately long for the patient population in the model. Because of the short time horizon, no discounting was applied and this is appropriate. The model is constructed from the NHS perspective.



Healing time

The sponsor has identified three studies of conventional topical burn treatments and used the healing times as a surrogate for the conventional dressing treatment arm of their model (Caruso et al. 2006; Cuttle et al. 2007; Silverstein et al. 2011). The values range from 13 days to 18 days and the sponsor takes the median value of 15 days as their base case. As described above the patient populations in these studies are heterogeneous, however Cuttle et al. (2007) reports time to healing only for patients who did not require grafting (in a paediatric population). This is consistent with the patient population for Group A in the Decision Problem and indicates that the sponsor's estimate is appropriate. In the clinical evidence submission only Wood et al. (2012) reports healing time for burn wounds treated with conventional dressings. Their median time for 4 paediatric patients with scalds is 36.5 (18.5 - 47.7) days for approximately 4-5% TBSA.

The sponsor has used a percentage reduction in the healing time for conventional dressings to determine healing times for Biobrane alone, Biobrane plus ReCell and ReCell alone. The sponsor has chosen conservative estimates of a 30% reduction for Biobrane or ReCell alone and 40% reduction for ReCell plus Biobrane. Although the EAC has noted concerns with the basis for this choice (above) the sponsor has varied the values from 0-50% for all three. The EAC considers this approach appropriate given the paucity of data on which to base the model.

Requirement to be treated as an in-patient

The sponsor correctly identifies the range of factors that influence the decision for a patient to remain as an in-patient during treatment. However, they reason that treatment with ReCell alone means that the wound surface is covered and that only secondary dressings require a COD. The manufacturer's instructions indicate that primary and secondary dressings should remain in place for 5 days. Clinical advisers indicate that the first COD and wound inspection occurs at 2-5 days post surgery. Biobrane adheres to the wound and is not removed until it lifts away from the surface as healing occurs. The EAC concludes that there is little evidence to support the assumption that the use of ReCell alone contributes to an earlier discharge.

The sponsor has adopted "arbitrary values" of 50% in-patient care for conventional dressing and 25% for the other 3 treatment arms. The EAC considers these to be high given the clinical opinions provided to the sponsor. However, as none of the respondents provided an answer to the question about proportions of patients we have no basis to choose other values.

Probability of skin grafting

The sponsor states that review of the burn injury at 10-12 days will determine the requirement for delayed skin grafting. They have used data from published studies on topical burn treatments to determine that 30% of burns treated with conventional dressings will require later SSG (Caruso et al. 2006; Cuttle et al. 2007; Ostlie et al. 2012; Silverstein et al. 2011). Estimates from two of the sponsor's clinical advisers indicates a graft rate of 5-10% for conventional dressings. The EAC agrees with the sponsor that the small number of patients in Wood et al. (2012) and the expectation that these injuries would require grafting means that the data from this study cannot be used reliably

here. The sponsor has referred to information from their clinical advisers. The pattern is mixed and is presented in Table 12.

Resource identification, measurement and valuation

The sponsor states (section 9.3.1 of sponsor submission) that burns are excluded from the Payment by Results (PbR) tariff and that there are no burns-specific codes in HRGv4. However NHS Reference Costs includes Health Resource Group (HRG) codes and data on burns (Department of Health 2012). NHS reference data is potentially valuable for validating the results of the model.

In the model a small number of published cost analyses on general burns care and the [REDACTED] are the main source of resource use and valuation data, supplemented by the opinions of a panel of four experts. Of the four experts chosen, one is the inventor of ReCell with a potential conflict of interest and is based in Australia. Whilst it is reasonable to approach such an expert with extensive knowledge of the product, the conflict of interest remains and should be noted and taken into consideration when interpreting the results. The other three experts surveyed by the sponsor are likely to be familiar with standard UK practice (one has worked in the UK, but also in Australia). The EAC considers the expert opinion from the Australian expert to be less pertinent to UK practice.

Technology and comparator costs

Summary of variables applied in the cost model

Table C5 in the sponsor submission lists the model inputs.

The proportion of patients treated as in-patients is the first set of inputs and the source of the data is the expert opinion questionnaire. None of the experts directly answered the question, indicating the difficulty in quantifying this. Two of the experts responded that for all of the treatment options, the patient may go home after the first dressing change if all is going well. The third expert gave estimates of length of stay for each of the treatment groups. Clarifying comments from the third expert indicate that with conventional dressings the patient is more likely to require morphine analgesia which requires admission to a ward for monitoring. The values in the sponsor's Table C5 appear to have been based on this comment. Given the uncertainty in the values it is essential to include robust sensitivity analysis for this parameter.

The proportion of patients progressing to SSG is based upon expert opinion for all of the treatments except conventional dressings. For conventional dressings the source is four studies (3 from the USA and one from Australia) from the sponsor's searches for clinical and economic data. The patient population in these studies does not match the scenario presented to the expert panel in the questionnaire and varies between studies. For example one study includes partial thickness burns of 5-40% TBSA (Caruso et al. 2006), and another 2.5-20% TBSA (Silverstein et al. 2011). The third study patients had burns up to 25% TBSA (Ostlie et al. 2012) and the fourth paper only reported the mean TBSA of the two groups as 4.4% and 5.2% (Cuttle et al. 2007). Therefore using the studies may over-estimate the proportion of patients requiring SSG compared with the expert view for alternative



treatments because the patient populations in the studies include more severe cases. The sponsor asked the expert panel for their opinion on this question and the responses are summarised in Table 12.

Table 12: Expert opinion - proportion of patients requiring SSGs

	Expert 1	Expert 2	Expert 3	Expert 4 (Non-UK)*
Conventional dressings	5%	10%	(no response)	Many may need surgery depending on initial assessment
Biobrane alone	<5%	10%	same	50% (trial)
ReCell	<5%	5-10%	no experience	I would expect very few
ReCell + Biobrane	<5%	5-10%	reduced by 25-50%	none in trial (small numbers)

* Refers to data from Wood et al. 2012.

The sponsor’s base case values (conventional dressings or Biobrane alone - 30%, ReCell or ReCell plus Biobrane - 10%) seem higher than those of the sponsor’s UK experts, but there did appear to be agreement from the experts that ReCell alone and in combination with Biobrane reduced the number of patients going on to SSG. The absolute values can be further explored in sensitivity analysis.

The mean time to 100% epithelialisation is the next variable in the sponsor’s Table C5. This is a clinical end point, rather than a resource variable, but is linked to resources through the length of stay (LOS) for in-patients and the number of dressing changes required up to the point of healing because of assumptions in the model. The sources for the LOS used in the conventional dressings arm of the model are the same four studies used to determine the proportion of patients progressing to SSG, and the same limitations apply. None of the studies are from the UK, and the populations are heterogeneous.

The LOS for the other interventions is calculated from a fixed percentage reduction in healing times. This is based on Wood et al. (2012), which included a total of 13 patients in the three arms of the trial. This showed a reduction in median time to heal from 36.5 days with conventional dressings (n=4) to 16 days for Biobrane only (n=4) and 16 days for Biobrane plus ReCell (n=5). The time to heal using conventional dressings is considerably longer than in the sponsor’s model (15 days). It does not necessarily follow that the same percentage reduction in healing time would be achieved for the population in the model.

The other study cited to justify the reduction in LOS is Echlin et al. (2012a). The description of the study identified as Echlin (2012a) in section 9.2.1 appears to correspond to another paper, Echlin et al. (2012b). Echlin et al. (2012b) is a conference abstract of a case series that additionally reports an



intra-patient comparison in 2 patients between ReCell and conventional treatment of graft donor sites. The sponsor acknowledges that the data from these two studies is not sufficiently robust to generate estimates of healing times. The sponsor therefore set baseline healing rate reduction for Biobrane or ReCell alone at 30% and in combination at 40% whilst undertaking wide sensitivity analysis from 0-50% for all three.

Wood et al. (2012) does not include a treatment arm for ReCell alone, therefore it does not provide evidence for a healing time reduction of 30%. In this small study there was a substantial reduction in healing time between both Biobrane alone and Biobrane plus ReCell compared with standard dressings (no statistical testing). There is minimal evidence for reduced healing time for ReCell alone from Hiller (Hiller et al. 2013), but this is an abstract of a case series (n=5) from conference proceedings and contains little detail. The abstract claims ‘acceleration in epithelialisation and healing time’. Rennekampff et al. (2011) gives a healing time of 7-9 days for ReCell in a case series of 5 patients, but as there is no comparator it is not possible to say if this is reduced (this may be the same study as (Hiller et al. 2013). Other clinical evidence is for Group B in the Decision Problem.

Cost of resources

The sponsor’s cost of re-dressing using conventional dressings [redacted] based on the [redacted]

[redacted] Although a stay in ITU is not excluded in the scope, the sponsor has excluded this from the [redacted] model.

[redacted] Uncertainties can be explored in sensitivity analysis.

For secondary dressing changes in the other treatment arms, the sponsor estimated the cost to be £25 based on assumption of 30 minutes of nurse time plus consumables. Again the derivation of this figure is unknown. The sponsor’s expert advisers were asked about the proportion of patients requiring a general anaesthetic (GA) for conventional and secondary dressing changes. Two of the UK advisers responded ‘rare’ and ‘zero’ for both types of dressing change. The third UK adviser indicated that greater than 50% of patients would require a general anaesthetic for re-dressing using conventional dressings, but less than 5% for Biobrane or Biobrane plus ReCell. (They did not respond



to this question on the proportion of patients requiring GA for ReCell alone.) Again, it is not clear if these responses represent a genuine diversity of practice. It is feasible that differences in the cost of re-dressing arise because changing conventional dressings is more painful and hence more likely to be undertaken under general anaesthetic, by more highly paid staff e.g. medical consultants, or takes longer because of the pain. It is not clear that the two costs have been calculated on the same basis or that they are comparable. Therefore this will require scrutiny in the sensitivity analysis.

The cost of ReCell is given as £950 per 320 cm² and the cost of Biobrane is £60.80 per 320 cm² treated. These values have been verified by the EAC.

- The general hospital costs in the model are taken from the [redacted] daily bed cost in the burns unit [redacted]
- daily staff cost in the burns unit (£ [redacted])
- hourly cost of theatre time (£ [redacted])

[redacted]

[redacted] The EAC has compared these figures with the staff costs published in Curtis (2012) and

[redacted] £35 per hour for a nurse on a 24 hour ward in Curtis (2012), and the Consultant Surgeon is [redacted] £147 per hour [redacted]

[redacted]

[redacted] In the NHS Reference Costs, the national average cost of an excess bed day for the burns codes JB12B, JB13B and JB21B are £583, £554 and £516 respectively (Department of Health 2012).

[redacted]

Hemington-Gorse (2009) conducted a top-down cost analysis of the Welsh Burns Unit at Morriston Hospital, Swansea. Unit costs were calculated as shown in Table 13. The EAC has converted the currency to GBP and adjusted for inflation. The values used in the model compare reasonably well with these.

Table 13: Unit costs from Hemington-Gorse et al. (2009)

Resource	Euros 2008	GBP 2008	GBP 2013
Low dependency ward	€477 per day	£379.69	£429.01



Theatre time	€6660 per hour	£5301.36	£5990.00
COD	€200	£159.20	£179.88
ITU bed	€2961	£2356.96	£2663.12

In Table C5 of the sponsor submission, the overall cost of an SSG is derived from time to healing outcomes from Ostlie (2012) a study comparing two different topical treatments, based in the USA. A third of patients went on to have skin grafts. The average LOS for all patients was 11 days, but the sponsor has used this as evidence of graft healing at 11 days following operation. This is inappropriate. Mean time to healing for a burn treated with SSG is reported in Gravante et al. (2007) as 12 days (for 320 cm² TBSA) and in Rawlins (2011a, etc) as 48 days (approximately 10-25% TBSA).

The sponsor states that the overall SSG cost is calculated based upon 30 minutes in the operating theatre, discharge at 4 days followed by secondary dressing changes every other day. The clinical evidence is in reasonable agreement with these values; operating times of 20 minutes time (Gravante et al. 2007) and 58 minutes (Rawlins 2013).

Cost per treatment/patient associated with the technology in the cost model

The list price for ReCell is given in Table C6 of the sponsor submission as £950 per pack, each of which can treat up to 320 cm². The base case in the model is based on the use of 2 packs to treat 640 cm². There are no consumables, maintenance or training costs in the model. This is appropriate since the manufacturer provides training and because the ReCell device is single use. The only additional cost identified by the sponsor is for an additional 10 minutes in the operating theatre at the initial procedure for debridement and dressing.

Cost per treatment/patient associated with the comparator technology (standard care)

The sponsor has based the cost per treatment/patient on a 10 day in-patient stay with re-dressings every 2 days at a cost of £166 each (Table C7a of sponsor submission). The reference given to justify the cost is

[Redacted text]

Of the UK experts two indicated that patients having conventional dressings go home after 2-3 days, depending on pain and if the wound is healing well. This is consistent with the NHS reference data under codes JB13B 'Other burn with other procedure, without major critical care' (mean LOS 2.88 days) and JB21B 'Other burn without other procedure, without major critical care' (mean LOS 2.28 days)(Department of Health 2012). The third UK expert indicated LOS to be 7-14 days for conventional dressings. These differences may relate to real variation in practice or to a different understanding of the patient population under consideration. In free text comments the third expert indicated that their responses related to burns ≥ 10% TBSA, whereas the sponsor asked the experts about burns 5-10% TBSA and this is indicated as an assumption of the model. Therefore it is likely that this is the source of difference in the responses.

[Redacted text]

Also, the mean LOS for moderate/severe burns (the lowest category to be associated with a Burns Unit) provided in the International Burn Injury Database is 15.3 days (NBCG 2008).

Cost per treatment/patient associated with the comparator technology (Biobrane)

The only additional input not yet considered in the Biobrane arm of the model is the cost of Biobrane. The EAC has checked the sponsor's value of £60.80 per 320 cm² and found it to be correct.

Cost per treatment/patient associated with the comparator technology (Biobrane plus ReCell)

There are no additional inputs for Biobrane plus ReCell.

Sensitivity analysis

The range of values tested in sensitivity analysis was considered by the EAC to be too narrow for some inputs where there is considerable uncertainty. There is considerable uncertainty regarding the sponsor's value of 10% of patients progressing to SSG for ReCell. The sponsor's sensitivity analysis considered the range 5%-20%. The EAC considered this should be extended to 30%, to examine the case where there is no difference between ReCell and standard care. The EAC considered that there was uncertainty around the cost of dressing changes, for conventional dressings and secondary dressings, and therefore extended the range in sensitivity analysis for these inputs.

4.3 Results of de novo cost analysis

Base-case analysis results

The EAC checked the model outputs and found no errors in the base case calculation. Overall Biobrane is the lowest cost, followed by Biobrane plus ReCell as reported in Tables C11a and C11b in the sponsor's submission. The lower costs of Biobrane arise because of the considerably lower technology costs compared with the alternatives, the reduced number of dressing changes and reduced healing time. ReCell is cost saving compared with conventional dressings in the sponsor's base case analysis. Cost savings for ReCell are driven by the reduction in the proportion of patients requiring SSG following ReCell, and the shorter healing time. Cost savings also depend on the differential dressing costs between changing conventional dressings and changing secondary dressings with ReCell.

Sensitivity analysis results

The sponsor's sensitivity analysis was checked by the EAC and discrepancies were found with the reported results in Tables C13a-C13d in the sponsor submission. The EAC calculated values are given in Table 14 to Table 17 below where there are differences with the reported values.



Table 14: ReCell differences from table C13a of sponsor submission

Variable	Range tested	Total cost per patient	
		Low EAC (sponsor)	High EAC (sponsor)
Proportion of patients treated as an in-patient	25% - 75%	£7891 (£7,106.82)	£ 10,515 (£9,205.79)

Table 15: ReCell plus Biobrane differences from table C13b in the sponsor's submission

Variable	Range tested	Total cost per patient	
		Low EAC (sponsor)	High EAC (sponsor)
Proportion of patients treated as an in-patient	25% - 75%	£7787 (£7,125.69)	£9991 (£8,889.33)

Table 16: Conventional – differences from table C13c in sponsor submission

Variable	Range tested	Total cost per patient	
		Low EAC (sponsor)	High EAC (sponsor)
Proportion of patients progressing to SSG	5% - 20%	£8529 (£8,872.72)	£9137 (£9,989.47)
Mean time to 100% re-epithelialisation	7.5 – 15 days	£7476 (£8,991.87)	£9542 (£10,369.12)



Table 17: Biobrane differences from Table C13d in the sponsor submission

Variable	Range tested	Total cost per patient	
		Low EAC (sponsor)	High EAC (sponsor)
Proportion of patients treated as an in-patient	25% - 75%	£6398 (£5,621.02)	£8991 (£7,695.16)
Proportion of patients progressing to SSG	5% - 20%	£4914 (£5,507.54)	£5805 (£6,993.01)

As the EAC considers that there is no supporting evidence that ReCell reduces the percentage of patients progressing to SSG we extended the range of the sensitivity analysis for this in the ReCell arm from 5-20% to 5-30%. If 30% of patients in the ReCell group progress to SSG, the total cost for ReCell increases to £9,079 but ReCell remains cost saving compared with conventional dressings (£9,543).

The EAC extended the range of values tested for the costs of COD; from £83-£249 to £25 -£249 for conventional COD and from £12.50-£37.50 to £12.50- £166 for secondary COD. ReCell remained cost saving compared with standard dressings. The results are shown in Table 18-Table 21 below.

Table 18: EAC’s one-way sensitivity analysis – ReCell alone (cf. Table C13a)

Variable	Range tested	Total cost per patient	
		Low EAC (sponsor)	High EAC (sponsor)
Proportion of patients treated as an in-patient	25%-75%	£7891 (£7106.82)	£10,515 (£9205.79)
Proportion of patients progressing to SSG	5% - 30%*	£7,596.84	£9079
Costs of resources.			
Conventional dressing change (cDressing)	£25* - 249	£7821	£7,933.43
Secondary dressing change (cDressminor)	£12.50 -£166*	£7,826.62	£8628

* Modified by EAC



Table 19: EAC’s one-way sensitivity analysis – ReCell plus Biobrane (cf. Table C13b)

Variable	Range tested	Total cost per patient	
		Low EAC (sponsor)	High EAC (sponsor)
Proportion of patients treated as an in-patient	25% - 75%	£7787 (£7,125.69)	£9991 (£8,889.33)
Costs of resources.			
Conventional dressing change(cDressing)	£25* - 249	£7716	£7,828.55
Secondary dressing change (cDressminor)	£12.50 -£166*	£7,730.20	£8428

* Modified by EAC

Table 20: EAC’s one-way sensitivity analysis – conventional dressings (cf. Table C13c)

Variable	Range tested	Total cost per patient	
		Low EAC (sponsor)	High EAC (sponsor)
Costs of resources.			
Conventional dressing change(cDressing)	£25* - 249	£8379	£10,227.52
Secondary dressing change (cDressminor)	£12.50 -£166*	£9,542.77	£9542

* Modified by EAC

Table 21: EAC’s one-way sensitivity analysis – Biobrane (cf. Table C13d)

Variable	Range tested	Total cost per patient	
		Low	High
Proportion of patients treated as an in-patient	25% - 75%	£6398 (£5,621.02)	£8991 (£7,695.16)
Costs of resources.			
Conventional dressing change(cDressing)	£25* - 249	£6187	£6,523.32
Secondary dressing change (cDressminor)	£12.50 -£166*	£6,334.14	£7128

* Modified by EAC

The sensitivity analysis showed the model to be very robust when each parameter is considered in isolation. The cost ranking for each treatment arm in the model remained consistent; Biobrane

alone, ReCell plus Biobrane, ReCell alone and conventional dressings. No probabilistic sensitivity analysis was undertaken due to lack of data on which to base the distributions.

Scenario analysis

The sponsor included scenarios based upon changing several inputs simultaneously to model a number of clinical scenarios. The scenarios were somewhat limited by the structure of the model:

- TBSA was reduced from 640 cm² to 320 cm²
- TBSA was increased from 320 cm² to 1280 cm²
- Hospital costs decreased by 25%
- Hospital costs increased by 25%
- All benefits reduced by 50% (proportion of patients remaining as in-patients, proportion of patients who have delayed grafting and time to heal)

Table C14 of the sponsor submission gives the results of the scenario analysis. There is an error in Table C10.2 of the sponsor submission. The bed cost in the base case is given as £166, whereas this is the base case cost of a dressing change and the bed cost is £152. The scenarios with “hospital costs reduced by 25%” were run by the sponsor with incorrect values. The EAC re-ran the scenarios with the correct inputs. In the scenario with “all benefits reduced by 50%” the sponsor did not change the percentage of patients requiring SSG in the Biobrane group (from the base case value, 30%). The EAC re-ran the scenario with the treatment effect for Biobrane reduced by 50%. The results of these changes are in Table 22-Table 23.

Table 22: EAC’s correction for scenario Table C14 – cost per patient

Scenario	Total cost per patient EAC (sponsor)			
	ReCell	ReCell + Biobrane	Conventional	Biobrane
TBSA = 320 cm²	£5537	£5534	£5514	£4391 (£4491)
TBSA=1280 cm²	£14,402	£13,870	£15,550	£10,684
Benefits reduced by 50%	£9311	£9277	£9542	£8235 (£7433)
Hospital costs reduced by 25%	£6447 (£7595)	£6395 (£6530)	£7499 (£7492)	£4924 (£5060)
Hospital costs increased by 25%	£9336 (£9185)	£9179 (£9041)	£11,586	£7873 (7734)



Table 23: EAC’s correction for scenario Table C14 – incremental cost (grey shading indicates cost saving for ReCell or ReCell plus Biobrane)

Scenario	Incremental cost EAC (sponsor)			
	ReCell vs conventional	ReCell+Biobrane vs conventional	ReCell vs Biobrane	ReCell+Biobrane vs Biobrane
TBSA = 320 cm ²	£23	£20	£1146 (£1046.21)	£1143 (£1042.86)
TBSA=1280 cm ²	-£1148 (-£1696.12)	-£1680 (-£2228.12)	£3718	£3186
Benefits reduced by 50%	-£231	-£265	£1076 (£1878.53)	£1042 (£1843.70)
Hospital costs reduced by 25%	-£1052 (£103.12)	-£1104 (-£961.99)	£1523 (£2535.68)	£1471
Hospital costs increased by 25%	-£2250 (-£2402.56)	-£2407 (-£2546.99)	£1463 (£1450.93)	£1306

In all of the scenarios presented, ReCell was cost saving compared with conventional dressings, except for the smaller wound size of 320 cm² TBSA when ReCell and ReCell plus Biobrane were more costly than conventional dressings. In all of the other scenarios Biobrane was the lowest cost option followed by ReCell plus Biobrane, ReCell alone and conventional dressings. The cost savings for ReCell and ReCell plus Biobrane compared with standard dressings in the scenarios “Hospital costs increased by 25%” and “TBSA=1280cm²” were lower after the corrections were applied.

The scenarios allowed the sponsor to change several model inputs simultaneously. The results of the scenario analyses showed the model to be robust.

Model validation

Sponsor’s validation

The sponsor validated the model using a

[REDACTED] The base case values in the model (£7891.93 ReCell, £6397.82 Biobrane, £7787.05 ReCell + Biobrane, £9,542.77 conventional dressings)

It would be better to find an alternative source for validation. The EAC considers the NHS Reference Costs to be an appropriate set since the sponsor did not use this source in the model and since it includes data from many UK centres (Department of Health 2012).

Validation with NHS Reference Costs

In the 2011-12 data the relevant codes are for ‘major burns’ (>20% TBSA) or ‘other burns’. For comparison with the model the EAC has considered the data for ‘other burns’ given in Table 24. The base case results for conventional dressings in the sponsor’s model are at the higher end of the inter-quartile range (IQR) for patients coded JB12B. The code is for patients having one graft procedure whereas in the model base case only 30% of patients having conventional dressings proceed to SSG. Therefore one would expect the base case costs to be lower. Average LOS in the model base case is 15 days, but in the patients coded JB12B it was 7.68 days. This may be explained by the sponsor’s assumption that in-patients remain in hospital until complete epithelialisation. In practice there may be earlier discharge points for some patients. The NHS Reference Costs for JB13B and JB21B give very much lower overall costs and LOS. The patient populations in these two codes are likely to include patients with smaller TBSA than those in the model. Taking into account the assumptions in the model and the differences in the populations, the base case results are reasonably consistent with the NHS Reference Costs.

Table 24: National reference costs for ‘other burns (Department of Health 2012)

Code	Description	National average unit cost (IQR)	Average LOS
JB12B	Other burn with one significant graft procedure without major CC	£8,046 (£6,400, £10,430)	7.68
JB13B	Other burn with other procedure , without major CC	£2,870 (£1,507, £3,771)	2.88
JB21B	Other burn without other procedure, without major CC	£1,749 (£939, £2,165)	2.28

Validation with Wood et al. (2012)

The results of the model differ from those in the cost analysis by Wood et al. (2012), which found that standard dressings were the lowest cost intervention, followed by ReCell plus Biobrane, and Biobrane alone was the most costly intervention. The key driver of the analysis was the number of bed hours occupied by the patients. The differences in these findings may be explained by:

- differences in clinical practice between UK and Australia
- differences in patient population
- geographical factors – some patients in Wood et al. (2012) were from remote areas, so could not be treated as out-patients



- small numbers of patients in Wood et al. (2012) – 13 in total for a 3 arm trial

4.4 Interpretation of economic evidence

Generalisability

The sponsor selected a population for the model, with the key parameter being the extent of the burn 640 cm² (5-10% TBSA). The burns were considered to be partial thickness at initial assessment. The sponsor considered that the model was not appropriate for burns greater than 20% TBSA, where there are more complex pathways. In more extensive burns, there is greater likelihood that patients require:

- skin grafting for full thickness injury
- ITU admission
- multiple trips to theatre

Together with the impracticalities of managing this burn size as an out-patient, the sponsor considers this takes larger burns out of the scope of the model. The EAC agrees with this distinction and this also fits with the decision problem in the scope.

The sponsor considered that the model was inappropriate for patients with burns <2% TBSA as they are unlikely to be treated in hospital. The EAC considers that this should refer to treatment in a specialist burns service rather than “in hospital”.

Strengths

Despite the paucity of data the sponsor has produced a model of a particular patient population that is fit for purpose and has been validated by the EAC. The lack of data is inherent in the topic and does not reflect any reluctance to undertake studies by the research community.

Sensitivity analysis was undertaken and supplemented by scenarios. The results are robust in the one-way sensitivity analysis and in the scenarios, except for the scenario with “TBSA=320 cm²”.

Weaknesses

There were some errors in the results of sensitivity analysis recorded in the submission.

The model relies quite significantly on an unpublished study [REDACTED] for cost data, which has not undergone peer review and for which little information about data acquisition and cost derivation is known.

The factors in the model that drive the cost saving for ReCell compared with standard dressings are the reduction in the proportion of patients requiring SSG and the shorter healing time. Evidence for these improved clinical outcomes is very limited (Wood et al. 2012) and restricted to ReCell in combination with Biobrane. Clinical evidence from Rennekampff et al. (2011) indicated the healing

time to be 7-9 days for ReCell, but there was no comparator in this case series of facial burns. Hiller (2013) indicated 'acceleration in epithelialisation and healing time' but there were few details in this abstract (also possibly the same study as Rennekampff et al. 2011).

It has been challenging for the sponsor to ensure that all of the model inputs are based on the chosen patient population. The evidence was taken from a small number of published and unpublished studies and expert opinion, often with different populations.

4.5 Additional work undertaken by the External Assessment Centre in relation to economic evidence

The EAC searched Econlit, but found no additional economic studies of ReCell.

The EAC completed a quality check on the Wood et al. (2012) study (Appendix 2).

The EAC completed a quality check on the sponsor's de novo model and submission (Appendix 4).

The EAC used NHS Reference Costs to validate the model results (Department of Health 2012). The results of the model were also compared with the results of a published cost analysis Wood et al. (2012).

The EAC ran some extended sensitivity analyses to investigate the impact of key inputs.

4.6 Conclusions on the economic evidence

- The sponsor's model is robust and shows cost savings for ReCell compared with standard dressings in partial thickness burns of size 640 cm² and 1280 cm².
- The evidence underpinning the model is very limited and some of it is of questionable suitability given the heterogeneity of the patient populations, the variable nomenclature used and the multiple ways of grouping burn injuries.
- The sponsor did not model Group B in the Decision Problem - 'Large area burns; full thickness or deep partial thickness burns including where mesh grafting is required'.

Impact on the cost difference between the technology and comparator of additional clinical and economic analyses undertaken by the External Assessment Centre

Corrections made by the EAC to some input errors in the model for the scenario in which "hospital costs reduced by 25%", changed the outcome for ReCell alone compared with standard dressings, from cost incurring (£103.12 sponsor result) to cost saving (-£1052 EAC result). For the scenario in which TBSA was increased to 1280 cm², the corrections reduced the cost saving for ReCell compared with standard dressings (-£1696.21 sponsor, -£1148 EAC). The full scenario results are in Table 22 to Table 23.



5 Conclusions

The case for this evaluation of ReCell is equivocal. The evidence is difficult to interpret as it is not strictly consistent with the patient population, intervention and comparator groups as defined in the Decision Problem. The available clinical evidence is sparse and mostly of a low level. Only two studies were large enough and were reported in sufficient detail to provide robust evidence (Gravante et al. 2007; Park et al. 2013). However these did not demonstrate clinical benefit for the burn wound (although a reduction in donor site size and pain was reported) or indicate a basis for resource saving (reduced LOS partially attributed to differences in wound severity). The evidence does appear to demonstrate that ReCell is at least as effective as other current treatments in the care of acute burns suitable for treatment at a specialist burn service in the UK. The evidence has not demonstrated superiority over current treatments but suggests that there is potential for increased clinical benefit in burn injuries of different severities.

The claimed benefits for the patient are:

- **A reduction in skin graft donor site size and depth:** ReCell necessarily requires a smaller donor site with respect to a split thickness skin graft taken to cover the same burn wound size. This is self-evident given the mode of use and is also supported by Gravante et al. (2007). However, in patients for whom a skin graft was not initially indicated (i.e. Group A) the use of ReCell necessarily creates an additional wound, albeit a small one. None of the clinical studies defined the depth of their SSGs beyond 'split thickness' – indicating the removal of the epidermis and top layer of the dermis. Therefore the EAC cannot comment on the relative depth of the biopsy.
- **Fewer complications, reduced morbidity and shorter healing time at the donor site:** This is outside the scope of this evaluation.
- **Shorter wound healing times at the recipient site:** Faster healing has not been demonstrated in Group B burn wounds (ReCell plus SSG versus SSG alone). Faster healing as reported in two small and statistically non-significant studies in comparison to SSG is not convincing and superiority against treatment with Biobrane alone is unclear.
 - **leading to improved burn wound aesthetic result with a lower likelihood of scarring and better match of skin colour and repopulation of melanocytes to reduce hypopigmentation in healed wounds:** This has not been demonstrated in the clinical evidence. One expert adviser indicated that they thought cosmetic outcomes were better than would otherwise be expected.
- **Reduced dressing change frequency (weekly rather than daily):** Fewer, or simpler (more superficial), dressing changes may result from use of ReCell, especially in the first few days following treatment. However, expert opinion indicates that standard care involves COD every 2-3 days and that this regime is maintained following the first COD. This outcome appears to be accepted for the use of Biobrane, and any superiority of ReCell (either in combination or alone) has not been demonstrated.



- **Less need for dressing changes under anaesthetic:** This outcome was not addressed by the clinical evidence and the responses from the sponsor's clinical experts were mixed; varying from no patients with any treatment requiring GA to more than 50% of conventional patients requiring GA (this latter for 10% or greater TBSA).

The claimed benefits to the healthcare system are:

- **Reduction in length of stay (LOS) in hospital:** The evidence provided for the economic model (Group A) is from a study of 13 patients that does not include ReCell alone, but only includes ReCell plus Biobrane (Wood et al. 2012). The sponsor's expert panel gave varying responses about time to discharge when asked about the proportion of patients suitable for discharge after initial treatment, but tended to indicate that most patients would be suitable for discharge following the first COD. This model input has been included in sensitivity analysis.
- **Weekly rather than daily dressing changes:** As above. However there is potential for a system benefit because of the potential for reduced cost due to changing secondary dressings (for patients treated with ReCell), compared with full conventional dressing changes. There is remaining uncertainty about the costs of these dressing changes, but this has been explored in the sensitivity analysis.
- **Earlier discharge and outpatient management:** As above for LOS.
- **Reduced need for re-dressings under anaesthetic:** As above. The basis for cost of conventional dressing changes is unclear from the sponsor's submission, so it is unclear whether COD under anaesthetic was included for a proportion of the dressing changes for conventional dressings.
- **Reduced requirement for external technical laboratory support:** Not included in the model.
- **Reduced likelihood of later readmission for corrective surgery as a result of improved aesthetic results:** This was not explored in the model timeframe.

For patients where there is no immediate need for mesh grafting no claims were made in the scope regarding a possible reduction in the need for SSG at 10-12 days. However this featured in the model and evidence was taken from Wood et al. (2012) supplemented by the survey of expert opinion. There were differences in the numbers from the experts on the proportion of patients that would progress to SSG, but agreement that fewer patients in the ReCell arm would require SSG compared with conventional dressings.

6 Implications for research

The available clinical evidence does not support the claims made in the scope partly due to the design of the studies that have been conducted. Due to the inherent heterogeneity in the patient population robust evidence is unlikely to be produced using tightly controlled criteria such as that used in Wood et al. (2012) unless the screened population is very large. Much larger, multi-centre studies may provide the numbers of patients necessary to overcome any baseline differences. This has the additional difficulty of attempting to standardise treatment protocols between centres and consultants. Although the number of specialist burn services in the UK (and therefore the number of consultant burn surgeons) is relatively small there may be significant variation in practice and preference between them.

Patient pathways are relatively well-established for the more superficial and the obviously deep partial or full-thickness burns. The more superficial burn injuries that would be treated in a specialist burns service (i.e. Group A in the Decision Problem) are the most common; around 4500 patients per year are suitable for treatment in a Burns Facility (NBCG 2008). But these are also the most likely to heal well without intervention using an expensive technology. This may explain the lack of published evidence in this patient group.

The clinical evidence is also scarce in the larger and deeper burns (Group B in the Decision Problem). Very little evidence was identified regarding the use of ReCell in combination with split thickness skin grafts. The reason for this is unknown as information from the sponsor's clinical advisers indicates that this practice is not uncommon. The relative rarity of patients in this population in the UK may contribute to the difficulty; only around 900 patients per year have burn injuries severe enough to warrant referral to a Burn Unit or Centre (NBCG 2008). Also the risk of significant morbidity and death increases with burn TBSA; one clinical adviser to the sponsor indicated an upper limit of around 60% TBSA as appropriate for ReCell.

Research in this patient population may be difficult to organise due to the need to co-ordinate multiple centres and involve a long recruitment time. Also due to the small numbers and heterogeneity it is likely that one or two patients with especially long recovery times and high resource use could heavily skew the data, particularly for resource use and cost information. Long term scar outcomes are particularly difficult to measure in more serious burns as patients may travel a significant distance to reach a specialised service.

Expert adviser opinion demonstrates the lack of agreement regarding the best treatment protocol for patients with mid-deep partial thickness wounds or burns in which the depth is indeterminate. Assessment of burn depth and healing potential is based primarily on clinical skill but can be assisted by the use of the moorLDI2 Burns Imager (NICE 2011). Research in this group in particular would be necessary to determine the effect of the use of ReCell on the need for delayed skin grafting.

A further difficulty in this area of research is the multiple interventions and comparators. There are four potential treatment arms defined in this evaluation, to treat burn wounds that can be characterised by both burn depth (or estimated time to heal, or anticipation to require grafting) and



burn area. These are further complicated by potential effects from variations in burn source (e.g. scald or flame burn) and patient age. This is a lot of variables to try and control and suggests the need to define a few areas in which incremental benefit may be demonstrated or refuted. The available evidence for the use of ReCell in acute burn wounds appears to demonstrate some clinical benefit from using Biobrane and/or ReCell in comparison to conventional dressings. However, whether ReCell confers any additional benefit when used in combination with or instead of Biobrane remains unknown.



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[REDACTED]

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Appendix 1 – EAC search strategy

Medline, Medline in progress and Embase

Search number	Search terms	Number of results
1	exp burns/	76189
2	(burn\$ or scald\$).tw.	119219
3	1 or 2	142849
4	recell.tw.	41
5	spray.mp.	31958
6	suspension.mp. or exp Suspensions/	144588
7	4 or 5 or 6	175315
8	3 and 7	1437
9	cell\$.mp.	8393187
10	8 and 9	338
11	Limit 10 to yr="1995-Current"	313

Web of Science, Scopus

Search terms		WoS results	Scopus results
Burn* AND	(spray OR suspension) AND cell	209	149
	OR		
	ReCell		

Cochrane

Search number	Search terms	Number of results
1	exp burns/	1100
2	recell.ti,ab,kw from 1995 to 2013	5
3	exp Suspensions/	312
4	spray*.ti,ab,kw	3054
5	suspension*.ti,ab,kw	2209
6	3 or 4 or 5	5228
7	cell*.ti,ab,kw	46833
8	6 and 7	352
9	2 or 8	355
10	1 and 9	4

Total number of unique records retained: 389



Appendix 2 – Quality checklist for Wood et al. (2012)

Study name Wood et al. (2012)		
Study design	Resource analysis alongside a randomised pilot study of Biobrane with or without autologous cell suspension compared with standard care for scald injuries in paediatric patients	
Study question	Response (yes/no/not clear/N/A)	Comments
1. Was the research question stated?	Yes	Resource analysis was a secondary objective
2. Was the economic importance of the research question stated?	No	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	No	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	No	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Cost consequences analysis. Clinical outcomes from within the study
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	Pilot study with very small numbers of patients.
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	n/a	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	n/a	
13. Were the details of the subjects from whom valuations were	Yes	



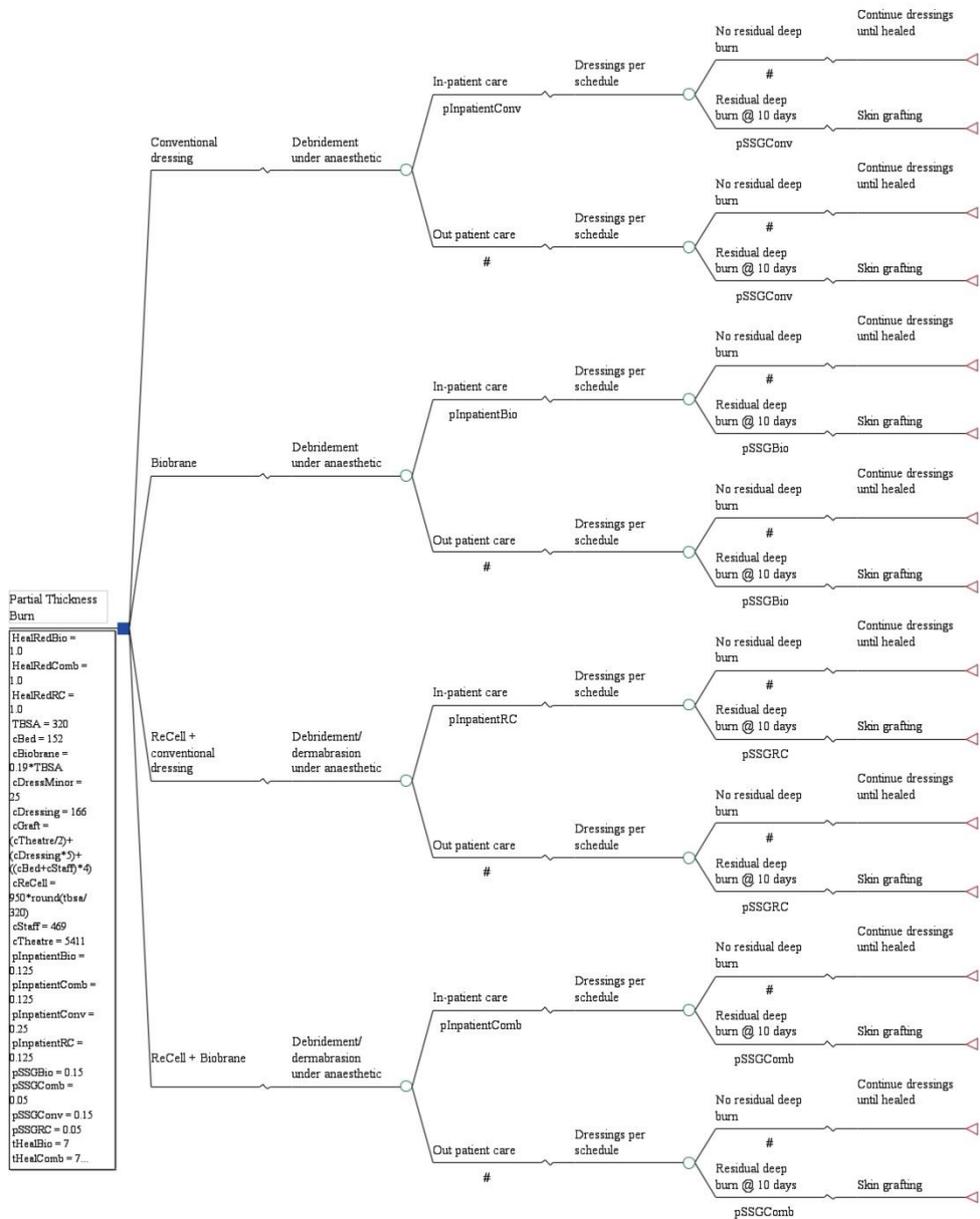
obtained given?		
14. Were productivity changes (if included) reported separately?	n/a	
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	No	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	Aus \$
20. Were details of any model used given?	n/a	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	n/a	
22. Was the time horizon of cost and benefits stated?	Yes	Acute episode only.
23. Was the discount rate stated?	n/a	
24. Was the choice of rate justified?	n/a	
25. Was an explanation given if cost or benefits were not discounted?	n/a	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	No	No sensitivity analysis
28. Was the choice of variables for sensitivity analysis justified?	n/a	
29. Were the ranges over which the parameters were varied stated?	n/a	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	n/a	
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as	Yes	



aggregated form?		
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		



Appendix 3 – Sponsor’s de novo economic model





Appendix 4 – Quality check on the sponsor’s de novo cost model

Study name ReCell sponsor model and submission		
Study design	Decision tree cost model	
Study question	Response (yes/no/not clear/N/A)	Comments
1. Was the research question stated?	Yes	The first decision problem in the scope.
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	NHS perspective
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Cost consequences analysis.
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	n/a	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	n/a	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	n/a	
13. Were the details of the subjects from whom valuations were obtained given?	n/a	
14. Were productivity changes (if included) reported separately?	n/a	
15. Was the relevance of productivity changes to the study question	n/a	



discussed?		
16. Were quantities of resources reported separately from their unit cost?	Yes	There was some aggregation. For example the cost of conventional dressing change was not disaggregated.
17. Were the methods for the estimation of quantities and unit costs described?	Yes	For most inputs.
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	n/a	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
22. Was the time horizon of cost and benefits stated?	Yes	Acute episode only – 21 days.
23. Was the discount rate stated?	n/a	
24. Was the choice of rate justified?	n/a	
25. Was an explanation given if cost or benefits were not discounted?	Yes	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	n/a	Decision tree
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	Results were given by technology cost, hospital cost and total cost.
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	



35. Were conclusions accompanied by the appropriate caveats?	Yes	The model is based on small studies and expert opinion.
36. Were generalisability issues addressed?	yes	Consideration of the extent to which the model applies to smaller and larger burns.
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

SCOPE

The ReCell spray-on skin system for treating skin loss, scarring and depigmentation after burn injury

1 Technology

1.1 *Description of the technology*

ReCell Spray-On skin is a rapid autologous cell harvesting, processing and delivery system for treating skin loss and preventing scarring and depigmentation in adults and children with burns. ReCell Spray-On skin is prepared by harvesting keratinocytes, melanocytes, fibroblasts and Langerhans cells which are normally contained within a thin split-thickness biopsy. The cells are processed into a suspension, which is delivered to the treatment area using a proprietary 'spray-on' application process and cells from the dermal-epidermal junction are able to rapidly proliferate and migrate in the wound bed. The regenerative nature of these skin cells promotes the growth of healthy skin to facilitate rapid healing. It takes approximately 20-30 minutes in total to collect the tissue and prepare and apply the cell suspension. The procedure is designed to be carried out by clinicians, without input from specialised laboratory staff.

1.2 *Regulatory status*

The ReCell received an updated CE mark in January 2013 (updated from first approval in March 2005) for autologous cell harvesting and topical spray application system.

1.3 *Claimed benefits*

The benefits to patients claimed by the sponsor are:

- a reduction in skin graft donor site size and depth
- fewer complications, reduced morbidity and shorter healing time at the donor site
- shorter wound healing time at the recipient site, leading to:
 - improved burn wound aesthetic result with a lower likelihood of scarring and better match of skin colour
 - repopulation of melanocytes to reduce hypopigmentation in healed wounds.
- reduced dressing change frequency (weekly rather than daily).
- less need for dressing changes under anaesthetic.

The benefits to the healthcare system claimed by the sponsor are a reduction in:

- length of stay in hospital; weekly rather than daily dressing changes allowing earlier discharge and outpatient management, thus reducing the costs of care

- need for re-dressings under anaesthetic, again reducing the costs of care
- requirement for external technical laboratory support
- likelihood of later readmission for corrective surgery as a result of improved aesthetic results.

1.4 Relevant diseases and conditions

Burns are relatively common and often extremely painful. Although most burns are minor, serious burns can result in disabling or disfiguring scarring, amputation or death. Recovery from a serious burn injury is associated with emotional and physical challenges and can have a significant impact on quality of life. A study of people hospitalised for burns found that around half changed job status as a result of their injury (Weichman and Patterson, 2004). Burns can also lead to increased fear, grief, anxiety and depression and in some cases, post-traumatic stress disorder. Scarring can lead to negative body image, feelings of social isolation and social stigma.

The majority of burn injuries are caused by heat, with around 5% caused by chemical injury or electrocution. The main causes of severe burn injury are flame burns and liquid scalds.

Around 250,000 people in the UK seek medical attention for burns each year. Of these, around 175,000 attend emergency departments and the UK admission rate is 0.29 per 1,000 cases of burns or smoke inhalation¹. In England, in 2011/12 there were 12,213 hospital admissions for burns and corrosions, of which 9,043 were emergency admissions. The average number of burns-related deaths in the UK each year is 300.

1.5 Current management

The treatment of burns can be considered in two phases; acute and reconstructive. The acute phase is focussed on the initial management of the patient's injury with the intention that burn wound healing will occur with minimal scarring and physical limitation. The reconstructive phase is focussed on improving the functional or visual impact of scarring, usually by surgical means, and may be undertaken months or years after the initial injury.

The first step in managing a burn injury is to assess the depth of the burn, the proportion of the body area involved and the site of injury. Burn depth is classified according to the level of skin or tissue affected.

Epidermal and superficial dermal wounds tend to heal without scarring or surgical intervention within 21 days. Deep dermal and full-thickness burns may require surgical excision (to remove the burnt skin and tissues) and skin grafting to ensure rapid healing, to minimise scarring and reduce complications. It is usual for surgical excision to take place within a day or two of admission. For mixed depth partial thickness scalds or burns, decision making normally occurs over 14-21 days unless the patient deteriorates before this. If after 14-21 days wounds are still unhealed skin grafts can be used to achieve a better cosmetic result.

Full-thickness burns more than 1cm in diameter will require skin grafts, as the regenerative components of the skin have been lost. Healing can only occur from the edges of the wound, but this will lead to contraction of the skin with poor cosmetic outcome and reduced mobility. Deep dermal burns are unlikely to heal within three weeks and will therefore often require grafting.

Skin grafts may be classified as partial or full-thickness grafts, depending on how much of the dermis is harvested by the surgeon. The clinical 'gold standard' for skin grafting is an autologous split-thickness graft taken from an area of unburnt skin. Grafts should ideally be taken from donor sites adjacent to the injury to improve the match with the surrounding skin. The donor site is itself a wound and will require treatment to ensure healing. If large grafts are required for extensive wounds the donated skin can be perforated (or meshed) to increase the surface area. The pattern of meshing can be visible after healing, so that sheet grafting is preferable to improve the cosmetic result. Allografting (using skin from another person, often a cadaver) and xenografting (using skin from animals) can also be used for temporary wound closure as these will ultimately be rejected by the body. Other alternatives to autologous grafts for deep partial-thickness and full-thickness wounds include artificial skin products.

2 Reasons for developing guidance on ReCell for treating skin loss, scarring and depigmentation after burn injury

The Medical Technologies Advisory Committee considered that ReCell Spray-on skin may be advantageous in the management of both partial thickness (where only ReCell is used) and large area burns (as an adjunct to skin grafting).

The Committee was advised that in small or partial thickness burns, using ReCell Spray-on skin may lead to improved healing with a reduction in the number of dressings required

The Committee considered that in full-thickness or deep partial thickness burns, the use of ReCell Spray-on skin may lead to a reduction in the size or number of skin grafts required as well as improved healing at the burn site. It concluded that benefits to patients may therefore include a reduction in pain and analgesia requirement as well as in complications including infection, blood transfusion requirement and death. It also considered that potential system benefits may include a reduction in procedural costs and hospital length of stay.

The Committee considered that ReCell Spray-On skin may provide particular benefits for patients who would currently be left with scarring at the burn site. This could avoid functional mobility complications in growing children, and psychological trauma for all patient groups as well as potentially avoiding corrective scarring operations.

The Committee was advised that ReCell Spray-On skin achieves better pigmentation to the skin as compared with skin grafting or cultured autologous cell applications.

3 Statement of the decision problem

	Scope issued by NICE
Population	<p>Adults or children treated in Burns Units or Centres for:</p> <ul style="list-style-type: none"> - Partial thickness burns including scalds caused by hot water where mesh grafting is not required - Large area burns; full thickness or deep partial thickness burns including where mesh grafting is required
Intervention	<ul style="list-style-type: none"> - Partial thickness burns including scalds caused by hot water: <ul style="list-style-type: none"> o ReCell Spray-on skin alone, or in combination with biosynthetic or standard dressings - Large area burns and full or deep partial thickness burns where mesh grafting is required: <ul style="list-style-type: none"> o skin mesh graft in combination with ReCell Spray-on skin.
Comparator(s)	<ul style="list-style-type: none"> - Partial thickness burns including scalds caused by hot water: <ul style="list-style-type: none"> o Biosynthetic dressings o Standard dressings - Large area burns; full or deep partial thickness burns where mesh grafting is required: <ul style="list-style-type: none"> o Skin mesh graft alone o Skin mesh graft plus biosynthetic dressing.
Outcomes	<p>The outcome measures to consider include:</p> <ul style="list-style-type: none"> • Speed of healing, including standard criteria such as number of days to full or 95% healing • Number of dressings to the wound with or without anaesthesia • Length of hospital stay per % of burn surface area • Wound infection rates • Degree of scarring including aesthetic and functional outcomes • Degree of pigmentation including aesthetic and functional outcomes • Re-admission to hospital for management of scarring • Transfusion rates during skin grafts • Number and size of donor sites • Growth rate in children • Surgical procedure and theatre time • Device-related adverse events.
Cost analysis	<p>Comparator(s):</p> <p>The choice of comparator will depend on burn type:</p> <p>Partial thickness burns including scalds caused by hot water: ReCell alone, or combination with biosynthetic or standard dressings, compared with:</p> <ul style="list-style-type: none"> • Biosynthetic dressings

	<ul style="list-style-type: none"> • Standard dressings <p>Large area burns; full or deep partial thickness burns where mesh grafting is required: Skin mesh graft plus ReCell compared with;</p> <ul style="list-style-type: none"> ○ Skin mesh graft alone ○ Skin mesh graft plus biosynthetic dressing <p>Costs will be considered from an NHS and personal social services perspective.</p> <p>The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared.</p> <p>Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.</p>
Subgroups to be considered	None identified
Special considerations, including issues related to equality	<p>Skin grafting in people with darker skin may result in a poorer colour match in the grafted area compared with normal skin. The ReCell Spray-on skin system may result in better colour matching of the resulting skin.</p> <p>The trypsin enzyme used to disaggregate the skin cells from the biopsy during the ReCell process is derived from pigs. This means that the treatment may be unacceptable to people from religious and cultural backgrounds that forbid contact with porcine material.</p>

4 Related NICE guidance

Published

- moorLDI2-BI: a laser doppler blood flow imager for burn wound assessment. Medical technology guidance MTG2 (March 2011) Available from <http://publications.nice.org.uk/moorldi2-bi-a-laser-doppler-blood-flow-imager-for-burn-wound-assessment-mtg2>

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Trauma services: service delivery of trauma services, NICE clinical guideline (publication expected October 2014)
- Major trauma: Assessment and management of major trauma, NICE clinical guideline (publication expected June 2015)

5 External organisations

5.1 Professional organisations

5.1.1 Professional organisations contacted for expert advice

At the selection stage, the following societies were contacted for expert clinical and technical advice:

- Association of Burns and Reconstructive Anaesthetists (ABRA)
- British Association of Plastic, Reconstructive and Aesthetic Surgeons (BAPRAS)
- British Burn Association
- Royal College of Surgeons

5.1.2 Professional organisations invited to comment on the draft scope

The following societies have been alerted to the availability of the draft scope for comment:

- Association of Burns and Reconstructive Anaesthetists (ABRA)
- British Association of Plastic, Reconstructive and Aesthetic Surgeons (BAPRAS)
- British Burn Association
- Royal College of Surgeons

5.2 Patient organisations

At the selection stage, NICE's Patient and Public Involvement Programme contacted the following organisations for patient commentary and alerted them to the availability of the draft scope for comment:

- Action for Sick Children
- Black Health Agency (BHA)
- British Red Cross
- British Skin Foundation (BSF)
- Changing Faces
- Children's Burn Trust (CBT)
- Dan's Fund for Burns
- Equalities National Council (ENC)
- Ethnic Health Foundation
- Let's Face It
- Muslim Health Network (MHN)
- NCT
- South Asian Health Foundation
- Specialised Healthcare Alliance
- WellChild

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The Committee was advised that in small or partial thickness burns, using ReCell Spray-on skin may lead to improved healing with a reduction in the number of dressings required

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3 Statement of the decision problem

	Scope issued by NICE
Population	<p>Adults or children treated in Burns Units or Centres for:</p> <ul style="list-style-type: none"> - Partial thickness burns including scalds caused by hot water where mesh grafting is not required - Large area burns; full thickness or deep partial thickness burns including where mesh grafting is required
Intervention	<ul style="list-style-type: none"> - Partial thickness burns including scalds caused by hot water: <ul style="list-style-type: none"> o ReCell Spray-on skin alone, or in combination with biosynthetic or standard dressings - Large area burns and full or deep partial thickness burns where mesh grafting is required: <ul style="list-style-type: none"> o skin mesh graft in combination with ReCell Spray-on skin.
Comparator(s)	<ul style="list-style-type: none"> - Partial thickness burns including scalds caused by hot water: <ul style="list-style-type: none"> o Biosynthetic dressings o Standard dressings - Large area burns; full or deep partial thickness burns where mesh grafting is required: <ul style="list-style-type: none"> o Skin mesh graft alone o Skin mesh graft plus biosynthetic dressing.
Outcomes	<p>The outcome measures to consider include:</p> <ul style="list-style-type: none"> • Speed of healing, including standard criteria such as number of days to full or 95% healing • Number of dressings to the wound with or without anaesthesia • Length of hospital stay per % of burn surface area • Wound infection rates • Degree of scarring including aesthetic and functional outcomes • Degree of pigmentation including aesthetic and functional outcomes • Re-admission to hospital for management of scarring • Transfusion rates during skin grafts • Number and size of donor sites • Growth rate in children • Surgical procedure and theatre time • Device-related adverse events.
Cost analysis	<p>Comparator(s):</p> <p>The choice of comparator will depend on burn type:</p> <p>Partial thickness burns including scalds caused by hot water: ReCell alone, or combination with biosynthetic or standard dressings, compared with:</p> <ul style="list-style-type: none"> • Biosynthetic dressings

	<ul style="list-style-type: none"> • Standard dressings <p>Large area burns; full or deep partial thickness burns where mesh grafting is required: Skin mesh graft plus ReCell compared with;</p> <ul style="list-style-type: none"> ○ Skin mesh graft alone ○ Skin mesh graft plus biosynthetic dressing <p>Costs will be considered from an NHS and personal social services perspective.</p> <p>The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared.</p> <p>Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.</p>
Subgroups to be considered	None identified
Special considerations, including issues related to equality	<p>Skin grafting in people with darker skin may result in a poorer colour match in the grafted area compared with normal skin. The ReCell Spray-on skin system may result in better colour matching of the resulting skin.</p> <p>The trypsin enzyme used to disaggregate the skin cells from the biopsy during the ReCell process is derived from pigs. This means that the treatment may be unacceptable to people from religious and cultural backgrounds that forbid contact with porcine material.</p>

4 Related NICE guidance

Published

- moorLDI2-BI: a laser doppler blood flow imager for burn wound assessment. Medical technology guidance MTG2 (March 2011) Available from <http://publications.nice.org.uk/moorldi2-bi-a-laser-doppler-blood-flow-imager-for-burn-wound-assessment-mtg2>

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Trauma services: service delivery of trauma services, NICE clinical guideline (publication expected October 2014)
- Major trauma: Assessment and management of major trauma, NICE clinical guideline (publication expected June 2015)

5 External organisations

5.1 Professional organisations

5.1.1 Professional organisations contacted for expert advice

At the selection stage, the following societies were contacted for expert clinical and technical advice:

- Association of Burns and Reconstructive Anaesthetists (ABRA)
- British Association of Plastic, Reconstructive and Aesthetic Surgeons (BAPRAS)
- British Burn Association
- Royal College of Surgeons

5.1.2 Professional organisations invited to comment on the draft scope

The following societies have been alerted to the availability of the draft scope for comment:

- Association of Burns and Reconstructive Anaesthetists (ABRA)
- British Association of Plastic, Reconstructive and Aesthetic Surgeons (BAPRAS)
- British Burn Association
- Royal College of Surgeons

5.2 Patient organisations

At the selection stage, NICE's Patient and Public Involvement Programme contacted the following organisations for patient commentary and alerted them to the availability of the draft scope for comment:

- Action for Sick Children
- Black Health Agency (BHA)
- British Red Cross
- British Skin Foundation (BSF)
- Changing Faces
- Children's Burn Trust (CBT)
- Dan's Fund for Burns
- Equalities National Council (ENC)
- Ethnic Health Foundation
- Let's Face It
- Muslim Health Network (MHN)
- NCT
- South Asian Health Foundation
- Specialised Healthcare Alliance
- WellChild

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical Technologies Evaluation Programme

Sponsor submission of evidence:

Evaluation title: The ReCell[®] Spray-On Skin[®] system for treating skin loss, scarring and depigmentation after burn injury

Sponsor: Avita Medical Ltd

Date sections A and B submitted:

Date section C submitted:

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Instructions for sponsors

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the Medical Technologies Evaluation Programme process for developing NICE medical technologies guidance. Use of the submission template is mandatory.

The purpose of the submission is for the sponsor to collate, analyse and present all relevant evidence that supports the case for adoption of the technology into the NHS in England, within the scope defined by NICE. Failure to comply with the submission template and instructions could mean that the NICE cannot issue recommendations on use of the technology.

The submission should be completed after reading the 'Medical Technologies Evaluation Programme Methods guide' and the 'Medical Technologies Evaluation Programme Process guide' available at www.nice.org.uk/mt. After submission to, and acceptance by, NICE, the submission will be critically appraised by an External Assessment Centre appointed by NICE.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly. For further information on disclosure of information, submitting cost models and equality issues, users should see section 11 of this document 'Related procedures for evidence submission'.

The submission should be concise and informative. The main body of the submission should not exceed 100 pages (excluding the pages covered by the template and appendices). The submission should be sent to NICE electronically in Word or a compatible format, not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level

of detail requested, but that is considered to be relevant to the case for adoption. Appendices will not normally be presented to the Medical Technologies Advisory Committee when developing its recommendations. Any additional appendices should be clearly referenced in the body of the submission. Appendices should not be used for core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the economic evidence section with 'see appendix X'.

All studies and data included in the submission must be referenced. Identify studies by the first author or trial ID, rather than by relying on numerical referencing alone (for example, 'Trial 123/Jones et al.¹²⁶', rather than 'one trial¹²⁶'). Please use a recognised referencing style, such as Harvard or Vancouver.

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

If a submission is based on preliminary regulatory recommendations, the sponsor must advise NICE immediately of any variation between the preliminary and final approval.

Document key

Boxed text with a grey background provides specific and/or important guidance for that section. This should not be removed.

Information in highlighted black italic is to help the user complete the submission and may be deleted.

The user should enter text at the point marked 'Response' or in the tables as appropriate. 'Response' text may be deleted.

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List of abbreviations

Abbreviation	Full format
SSG	Split (thickness) skin graft
TBSA	Total body surface area
MKT	Melanocyte-keratinocyte transplantation
RCT	Randomised controlled trial
VAS	Visual analogue scale

All abbreviations are also expressed in full the first time they appear in the text.

Section A – Decision problem

Section A describes the decision problem, the technology and its clinical context. There is also information about ongoing studies, regulatory information and equality issues.

Sponsors should submit section A before the full submission (for details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt)

1 Statement of the decision problem

The decision problem is specified in the final scope issued by NICE. The decision problem states the key parameters that should be addressed by the information in the evidence submission. All statements should be evidence based and directly relevant to the decision problem.

Table A1 Statement of the decision problem

	Scope issued by NICE	Variation from scope	Rationale for variation
Population	Adults or children treated in Burns Units or Centres for: <ul style="list-style-type: none"> a) partial thickness burns including scalds caused by hot water where mesh grafting is not required b) large area burns; full thickness or deep partial thickness burns including where mesh grafting is required 	None	
Intervention	<ul style="list-style-type: none"> a) ReCell Spray-On Skin alone, or in combination with biosynthetic or standard dressings b) Skin mesh graft in combination with ReCell Spray-On Skin 	None	
Comparator(s)	<ul style="list-style-type: none"> a) Partial thickness <ul style="list-style-type: none"> i. Biosynthetic dressings ii. Standard dressings b) Large area burns <ul style="list-style-type: none"> i. Skin mesh graft alone ii. Skin mesh graft plus biosynthetic dressing 	None	
Outcomes	Both indications <ul style="list-style-type: none"> i. Speed of healing ii. Number of dressings iii. Length of stay per % total body surface area (TBSA) iv. Wound infection rates v. Scarring: aesthetic and functional outcomes vi. Pigmentation: aesthetic and functional outcomes vii. Re-admission rates for scar management viii. Transfusion rates during skin grafting ix. Number and size of donor sites x. Growth rate in children xi. Surgical procedure and theatre time xii. Device-related adverse events 		
Cost analysis	Comparators: <ul style="list-style-type: none"> a) Partial thickness: ReCell alone vs: <ul style="list-style-type: none"> i. Biosynthetic dressings 		

	<ul style="list-style-type: none"> ii. Standard dressings <p>b) Large area burns: Skin mesh graft + ReCell vs:</p> <ul style="list-style-type: none"> i. Skin mesh graft alone ii. Skin mesh graft + biosynthetic dressings <p>Costing from the perspective of the NHS + personal social services Time horizon Sensitivity analyses</p>		
Subgroups to be considered	None		
Special considerations, including issues related to equality	<p>Effect of ReCell vs skin grafting on colour match in people with darker skin</p> <p>Use of porcine-derived trypsin in ReCell process</p>		

2 Description of technology under assessment

2.1 Give the brand name, approved name and details of any different versions of the same device.

ReCell[®] Spray-On Skin[®] C3RL01:EU

2.2 What is the principal mechanism of action of the technology?

ReCell is a stand-alone autologous cell harvesting device that enables a thin split-thickness skin biopsy to be processed to produce a mixed cell population for immediate delivery onto a prepared wound surface.

When an injury, such as a burn, results in loss of skin epithelium, healing and re-epithelialisation must proceed from residual cells at the wound edge. This process may take a considerable time and exposes the individual to risks of infection, scarring and hypopigmentation. It is widely acknowledged that a wound that takes in excess of 21 days to heal is more likely to be left with a hypertrophic scar¹. Split skin grafting (SSG), taking epithelium from healthy skin elsewhere in the body, may speed this process but is limited by the availability of suitable donor sites and is prone to resulting in poor aesthetic outcomes and large donor site scars. Another key issue is the available area for donor sites. If burns are extensive, a mesh graft can be used – this process allows expansion of the grafted skin to cover an area of up to 6 times the original donor area.

An alternative strategy is to culture sheets of keratinocytes from a biopsy of the patient's own skin. This circumvents the problem of available donor skin area, as there is no theoretical limit to the quantity of cells that can be produced. However, cell culture requires specialist laboratory facilities, is expensive and may take several weeks to yield sufficient cells to allow wound closure.

The ReCell device allows a small (up to 4 cm²), thin (0.15-0.20mm) split thickness shave biopsy to be physically and enzymatically broken down, yielding a viable suspension of mixed keratinocytes, fibroblasts and

melanocytes that can be immediately sprayed or dripped on to the de-epithelialised area. The process is rapid – around 30 minutes – and does not require specialist skills or facilities to carry out. A cell suspension derived from a 1 sq cm biopsy is sufficient to treat an area of around 80 sq cm, making it particularly valuable for patients with limited available healthy donor sites.

The other key advantage of ReCell is the presence of viable melanocytes in the harvested cells. This means that an excellent skin colour match can be achieved. Given that only a small area of biopsy is required (unlike SSG), it is usually not difficult to source this from close to the wound site, thereby optimising the chances of a good aesthetic result.

3 Clinical context

3.1 Provide a brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE.

Although ReCell has been used in a wide range of conditions requiring re-epithelialisation, for the purposes of the current guidance, only the management of burns is considered.

In England in 2011-12 there were 11,830 admissions with a burns-related diagnosis (ICD-10 categories T20.0 – T31.9: excluding corrosions). Of these, 8,744 were classified as emergencies and therefore are likely to reflect admissions for the acute management of flame burns and scalds ². Not all of these admissions will have been to specialist Burns Units or Burns Centres, as specified by the scope. Data from the International Burn Injuries Database (IBID) showed that, in 2007 (the most recent year for which data have been published), there were 5,086 qualifying admissions to specialist burns services in England and Wales, in addition to a further 2,837 cases managed as outpatients ³.

Severity of burns – and therefore the modes of treatment adopted – is assessed by a combination of factors related to the burn itself (depth, extent,

location) and the patient (age, comorbidities). Burns severity is an important measure as it is a major determinant of the length of hospital stay, which itself is a key driver of ultimate cost of care.

*Mean length of stay by burns severity*³

- Minor 0.9 days
- Moderate 8.8 days
- Moderate severe 15.3 days
- Severe 13.6 days
- Severe complex 35.2 days

The IBID results show that, out of 27,083 patients with a burn severity recorded over the period 2003-07, 43% were rated as moderate severity, while 17% were moderate severe, severe or severe complex. Patients with minor burns are likely to heal with simple conservative dressing strategies. Those at the higher severity levels (moderate and above) are more likely to be candidates for surgical intervention and therefore are potential users of ReCell.

- 3.2 Give details of any relevant NICE or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies specific subgroups and make any recommendations for their treatment. If available, these should be UK based guidelines.

A wide range of potentially relevant sources of clinical guidelines were searched – no pertinent guidance was found:

- NICE – no relevant guidelines
- Scottish Intercollegiate Guidelines Network – no relevant guidelines
- British Burn Association – no relevant guidelines
- European Burn Association - European Practice Guidelines for Burn Care issued in 2002 and updated in 2011⁴. Principally concerned with

service provision standards. No clinical guidance of relevance to this scope

- American Burn Association – Practice Guidelines for Burn Care issued in 2001⁵. Clinical guidance on a range of aspects of burns service provision and principles of care. No relevant content for this scope
- International Society for Burn Injuries – no relevant guidelines

3.3 Describe the clinical pathway of care that includes the proposed use of the technology.

We have been unable to identify any published general clinical pathways for the management of burns and the following is therefore based on information provided to us by clinicians involved in the management of burns. Specific treatment strategies will vary considerably according to individual clinical circumstances and the preferences and policies of the individual burns consultants. The strategy outlined here, therefore, should only be regarded as an expression of general principles of care.

Step 1 (0-2 days): Most patients with anything other than minor burns will be taken to theatre for cleaning and assessment of depth of injury under anaesthetic.

- Superficial dermal wounds thought likely to heal without specific intervention will be debrided and dressed according to local protocols (conventional dressing)
- Full-thickness burns will be dermabraded and early SSG applied
- Partial thickness injuries (including those of indeterminate depth) will be cleaned and debrided. Biological dressing (Biobrane) or conventional dressing applied with a view to reassessment at 7-10 days.

Step 2 (2-10 days): Patients generally remain on ward. Conventional dressings usually redressed daily. Depending on age of patient and extent of injury this redressing may be carried out under anaesthetic. In grafted patients, donor sites also actively managed.

Step 3 (10-12 days): Wound reassessed. If insufficient wound healing progress has been made, delayed skin grafting will take place at this stage. In patients with extensive wounds, limitations regarding the extent of available donor sites may mean that coverage has to be achieved in multiple stages once previous donor sites have healed sufficiently to allow further graft tissue to be taken.

Step 4 (3 months – 2 years): Post-discharge scar assessment. Aesthetic and functional status assessed. Remedial surgical intervention including further grafting may be scheduled at this stage to improve texture and colour of the scar.

3.4 Describe any issues relating to current clinical practice, including any uncertainty about best practice.

The use of early grafting varies considerably by unit, especially where wound depth is uncertain. Laser Doppler assessment of depth is used in some units, although practical issues make this technology difficult to implement particularly with young children.

Burn care is highly individualised, based on the characteristics of the injury and the patient themselves. There are often complicating factors. Use of ReCell is a shift towards early intervention which is disruptive to the procedures many surgeons have been undertaking since qualification. For 30 years surgeons have operated one way, now we are recommending another pathway.

3.5 Describe the new pathway of care incorporating the new technology that would exist if the technology was adopted by the NHS in England.

ReCell can be used at three distinct stages in the burns management process.

For patients with partial thickness burns, or those of indeterminate depth, harvested cells can be applied using ReCell at step 1, in order to maximise the chances of a wound re-epithelialising. This may result in excellent wound healing progress at step 2, or alternatively a lesser area of unhealed wound that requires delayed grafting. If ReCell is applied at step 1, dressings are left undisturbed until the reassessment at step 2. This incurs savings in terms of re-dressing costs and the requirement for associated anaesthetic/analgesics. Additionally, where the patient's condition is otherwise stable and social circumstances permit, a continued stay on the ward is not required and

patients can be discharged, with the 10-12 day reassessment taking place as an outpatient. This is both preferable to the patient and incurs substantial savings. Experience at Pinderfield's Hospital in Wakefield suggests that approximately 60% of patients not requiring early grafting can be treated in this way, with approximately 75% being discharged for subsequent outpatient management [personal communication Mr Jeremy Rawlins].

ReCell can also be used (at step 1 or 2) in combination with conventional mesh grafting for patients with areas of burn injury lacking confluent dermis. Mesh skin grafting involves mechanical perforation of a continuous sheet of harvested skin to result in a net-like appearance. The resulting mesh can then be stretched over the de-epithelialised area, with subsequent healing taking place due to migration of keratinocytes across the small interstices of the mesh. The mesh pattern may be retained in the final scar, yielding a cosmetically compromised result. Expansion of 2-3 times is clinically typical. In circumstances of limited donor availability wider (4:1, 6:1) may be used, which exacerbates the aesthetic issue and increases risk of graft loss/failure. By using ReCell to spray harvested autologous epithelial cells over the mesh network at the time of application, a thinner graft may be taken without incurring the usual additional risk of graft failure. The combination of thin graft and cell suspension together mitigate the persistence of the mesh-pattern scar, and also enables more routine use of widely meshed graft (and corresponding decrease to donor site area and morbidity).

Use of ReCell results in newly formed epithelium that can require up to approximately two weeks from initial closure to become mature and robust. This must be accounted for in the planning of post-operative care in terms of staff and patient education. Generally, this poses no cause for concern, however if there are clinical concerns relating to the patient's understanding of the post-operative care needed for a ReCell-treated burn injury area and the need for protecting the area from insult while the new skin matures, the short-term risk of re-injury may be mitigated by temporarily increasing use of protective dressings or by proactively combining ReCell with conventional graft (versus ReCell alone) in those areas which may be susceptible to

contact injury due to size or location (e.g. distal extremities, joints) and anticipated patient activity.

Thirdly, at step 4, where the healed scar is hypertrophic or hypopigmented, dermabrasion and application of colour-matched epithelial cells using ReCell can improve the final aesthetic result.

3.6 Describe any changes to the way current services are organised or delivered as a result of introducing the technology.

Earlier patient discharge will result in less need for nursing care on the wards. The number of dressing changes will also be reduced and performed in outpatients instead of inpatients. Training of the nursing team will be required to ensure they do not continue to change dressings on a daily basis as with other burn treatment options, and that appropriate care is taken of the newly regenerated skin whilst it fully matures.

The cell separation process using ReCell takes around 30 minutes once the skin biopsy has been taken. When use of ReCell is first put into practice, the procedure will add time to the surgery, however as surgical teams become more experienced with ReCell, the procedure will be incorporated in a parallel fashion with minimal impact on surgical time. In fact, once established, use of ReCell alone (in place of mesh skin grafting, as appropriate) saves on the length of time in surgery which has been shown as an independent predictor of length of stay⁶.

3.7 Describe any additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice.

None.

3.8 Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.

None

3.9 Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology.

It is unlikely that ReCell will completely remove the need for any related technologies, although where cell culture facilities are currently used, it is possible that these can be scaled down.

3.10 Describe how the NHS in England can disinvest from tests, investigations, interventions, facilities or technologies described in section 3.9 that would no longer be needed with using this technology.

Where cell culture is used, these are normally provided by commercial providers on a per patient basis. A reduction in use would therefore result in a simple decline in demand for this service, with no formal disinvestment strategy required.

4 Regulatory information

4.1 Provide PDF copies of the following documents:

- instructions for use
- CE mark certificate or equivalent UK regulatory approval such as EC declaration of conformity
- quality systems (ISO 13485) certificate (if required).

PDF copies of these documents should be submitted at the same time as section A.

4.2 Does the technology have CE mark for the indication(s) specified in the scope issued by NICE? If so, give the date that authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Yes. Authorisation under Directive 93/42/EEC on medical devices, Annex II (excluding Section 4) granted on 18 March 2005. Current certificate valid until 23 January 2017

4.3 Does the technology have regulatory approval outside the UK? If so, please provide details.

Currently approved for use in: Australia, Canada, China, Croatia, European Member States, Hong Kong, Israel, Kuwait, Macau, New Zealand, Poland, Switzerland, Singapore, Taiwan and Turkey

4.4 If the technology has not been launched in the UK provide the anticipated date of availability in the UK.

n/a

4.5 If the technology has been launched in the UK provide information on the use in England.

ReCell is widely used within the NHS in both burns units and plastic surgery departments. The English centres with the greatest use are:

- Chelsea and Westminster Hospital, London – Burns and Plastics
- Guy's and St Thomas' Hospital, London - Plastics
- Broomfield Hospital, Chelmsford– Burns and Plastics
- Pinderfields Hospital, Wakefield– Burns and Plastics
- Queen Elizabeth Hospital Birmingham and Birmingham Children's Hospital – Burns and Plastics
- Nottingham University Hospitals, Nottingham – Burns and Plastics
- Frenchay Hospital, Bristol – Burns and Plastics
- Alderhey Children's Hospital, Liverpool – Burns and Plastics

5 Ongoing studies

- 5.1 Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months.

A study of ReCell Spray-On Skin for restoration of pigment in hypopigmented burn scars. Randomised controlled study (pilot), 20 patients, expected completion date is May 2014. Primary objective is to assess repigmentation with ReCell versus control at 3 and 6 months. Secondary objective, patient satisfaction levels.

- 5.2 If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

We are not aware of any other planned assessments

6 Equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to comply fully with legal obligations on equality and human rights.

Equality issues require special attention because of NICE's duties to have due regard to the need to eliminate unlawful discrimination, promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others.

Any issues relating to equality that are relevant to the technology under assessment should be described. This section should identify issues described in the scope and also any equality issues not captured in the final scope.

Further details on equality may be found in section 11.3 of this document.

6.1.1 Describe any equality issues relating to the patient population and condition for which the technology is being used.

Skin grafting in people with darker skin may result in a poorer colour match in the grafted area compared with normal skin. The ReCell Spray-On Skin system may result in better colour matching of the resulting skin.

The trypsin enzyme used to disaggregate the skin cells from the biopsy during the ReCell process is derived from pigs. This means that the treatment may be unacceptable to people from religious and cultural backgrounds that forbid contact with porcine material.

6.1.2 Describe any equality issues relating to the assessment of the technology that may require special attention.

None known

6.1.3 How will the submission address these issues and any equality issues raised in the scope?

The issue of skin pigmentation is an important aspect of the assessment of the aesthetic result of burns wound treatment. As ReCell is able to ameliorate this problem, it will be fully addressed in the submission.

The issue of porcine origin of biological elements that are integral to ReCell is well recognised. Biological dressings such as Biobrane – the other treatment modality specifically mentioned in the scope – also has porcine components and is therefore subject to the same limitation. We have spoken to consultants using both ReCell and Biobrane and we understand that individual patients and their families, once made aware of the situation, are comfortable making their own decision as to both products' use that is acceptable to their beliefs. We do not feel that formal NICE guidance on this issue is either practical or desirable and therefore we have not addressed it further in our submission.

Section B – Clinical evidence

7 Published and unpublished clinical evidence

Section B requires sponsors to present published and unpublished clinical evidence for their technology.

Sponsors should read section 6 of the Medical Technologies Evaluation Programme methods guide on published and unpublished evidence, available from www.nice.org.uk/mt

All statements should be evidence-based and directly relevant to the scope. Reasons for deviating from the scope should be clearly stated and explained in table A1.

Sponsors are required to submit section B in advance of the full submission (for details on timelines, see the NICE document ‘Guide to the Medical Technologies Evaluation Programme process’, available from www.nice.org.uk/mt

7.1 *Identification of studies*

Published studies

7.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature. Exact details of the search strategy used should be provided in section 10, appendix 1.

Search sources

The following sources were used:

- Electronic databases: MEDLINE (including Medline In Process); EMBASE; Cochrane Library. Detailed search strategy listed in section 10, appendix 1.
- Manufacturer’s database of known research projects.

- Hand search of abstracts lists for burns-related conferences over the past 5 years: British Burn Association; European Burn Association; American Burn Association; International Society for Burn Injuries.
- Hand search of reference lists from studies identified in the previous searches.

Search terms:

For the electronic database searches, the following strategy was used, suitably adapted to suit each database. The strategy was kept deliberately broad, as it was expected that the number of qualifying studies would be small, and therefore relatively easy to filter manually:

Burns [Subject Heading] OR (Burn* [Textword] OR Scald* [Textword])

AND

ReCell [Textword] OR (Autologous NEAR Cell NEAR Harvest*) [Textwords]

Time frame:

ReCell was developed in the late 1990s but its use has only become widespread over the past 5 years. In order to capture all possible publications, a time limit of 1995-present was used for all databases.

Subsidiary literature search – skin pigmentation

As one of the key claimed benefits of ReCell is its ability to yield an improved skin colour match compared with conventional treatments, a subsidiary literature search was carried out to identify published data specifically relating to the effect of ReCell on skin pigmentation. For this search, studies in clinical areas other than burns were included, in order to capture this element adequately. Although these studies fall outside the scope, we believe that this information is relevant to burns patients and is therefore worth capturing.

Search sources

The following sources were used:

- Electronic databases: MEDLINE (including Medline In Process); EMBASE; Cochrane Library. Detailed search strategy listed in section 10, appendix 1.
- Manufacturer's database of known research projects.
- Hand search of reference lists from studies identified in the previous searches.

Search terms:

For the electronic database searches, the following strategy was used, suitably adapted to suit each database:

Hypopigmentation [Subject Heading] OR Vitiligo [Subject Heading]

AND

ReCell [Textword] OR (Autologous NEAR Cell NEAR Harvest*) [Textwords]

Time frame: 1995 to present

Unpublished studies

7.1.2 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

Search sources:

- Manufacturer's database of known research projects.
- Personal contact with researchers responsible for meeting abstracts identified in the search for published studies

As electronic databases were not involved, no formal search strategy was required

7.2 Study selection

Published studies

7.2.1 Complete table B1 to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table B1a Selection criteria used for published studies

Inclusion criteria	
Population	Adults and children undergoing treatment for flame burns and scalds
Interventions	Autologous skin cell harvesting (ReCell) used either alone or in combination with other treatments
Outcomes	<ul style="list-style-type: none"> i. Speed of healing ii. Number of dressings iii. Length of stay per % TBSA iv. Wound infection rates v. Scarring: aesthetic and functional outcomes vi. Pigmentation: aesthetic and functional outcomes vii. Re-admission rates for scar management viii. Transfusion rates during skin grafting ix. Number and size of donor sites x. Growth rate in children xi. Surgical procedure and theatre time xii. Device-related adverse events xiii. Analgesic/anaesthetic use xiv. Other resource utilisation outcomes not specified above xv. Other patient-relevant outcomes not specified above
Study design	Systematic reviews with quantitative outcomes, Randomised controlled trials, non-randomised observational studies, comparative or non-comparative case series
Language restrictions	Any language
Search dates	1995 - 2013
Exclusion criteria	
Population	Patients undergoing treatment for indications other than flame burns or scalds
Interventions	Treatments not involving autologous skin cell harvesting
Outcomes	None explicitly excluded
Study design	Narrative reviews not including direct patient effectiveness data, single patient case reports, animal studies, in vitro studies
Language restrictions	None
Search dates	Pre 1995

7.2.2 Report the numbers of published studies included and excluded at each stage in an appropriate format.

Figure 1: PRISMA diagram for main search - burns

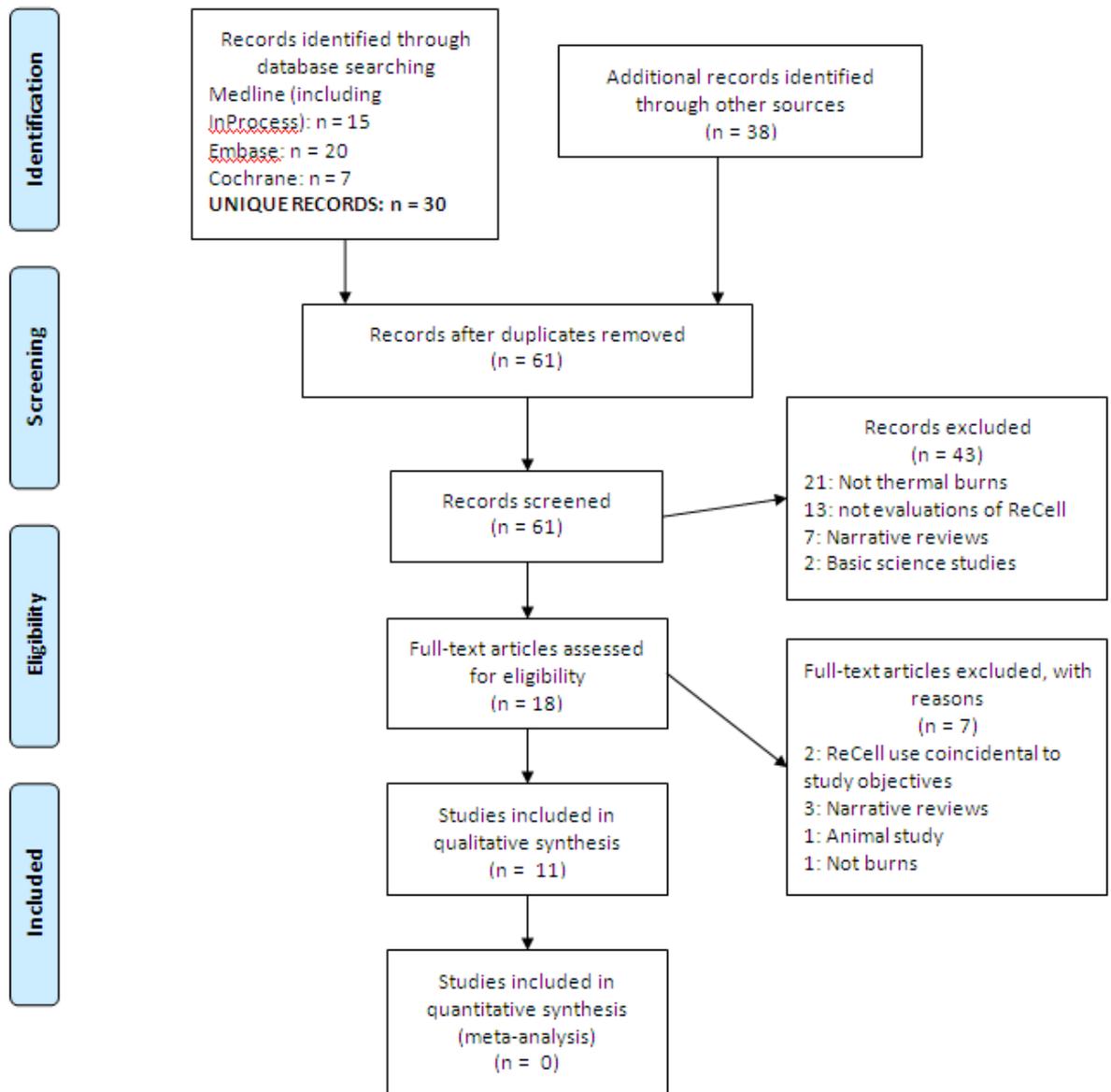


Table B1b Selection criteria used for published studies (subsidiary search)

Inclusion criteria	
Population	Adults and children undergoing treatment with ReCell for any reason
Interventions	Autologous skin cell harvesting (ReCell) used either alone or in combination with other treatments
Outcomes	Effect of treatment on pigmentation
Study design	Systematic reviews with quantitative outcomes, Randomised controlled trials, non-randomised observational studies, comparative or non-comparative case series.
Language restrictions	Any language
Search dates	1995 - 2013
Exclusion criteria	
Population	None
Interventions	Treatments not involving autologous skin cell harvesting
Outcomes	Anything other than effect on pigmentation
Study design	Narrative reviews not including direct patient effectiveness data, single patient case reports, animal studies, in vitro studies
Language restrictions	None
Search dates	Pre 1995

Figure 2: PRISMA diagram for subsidiary search – hypopigmentation

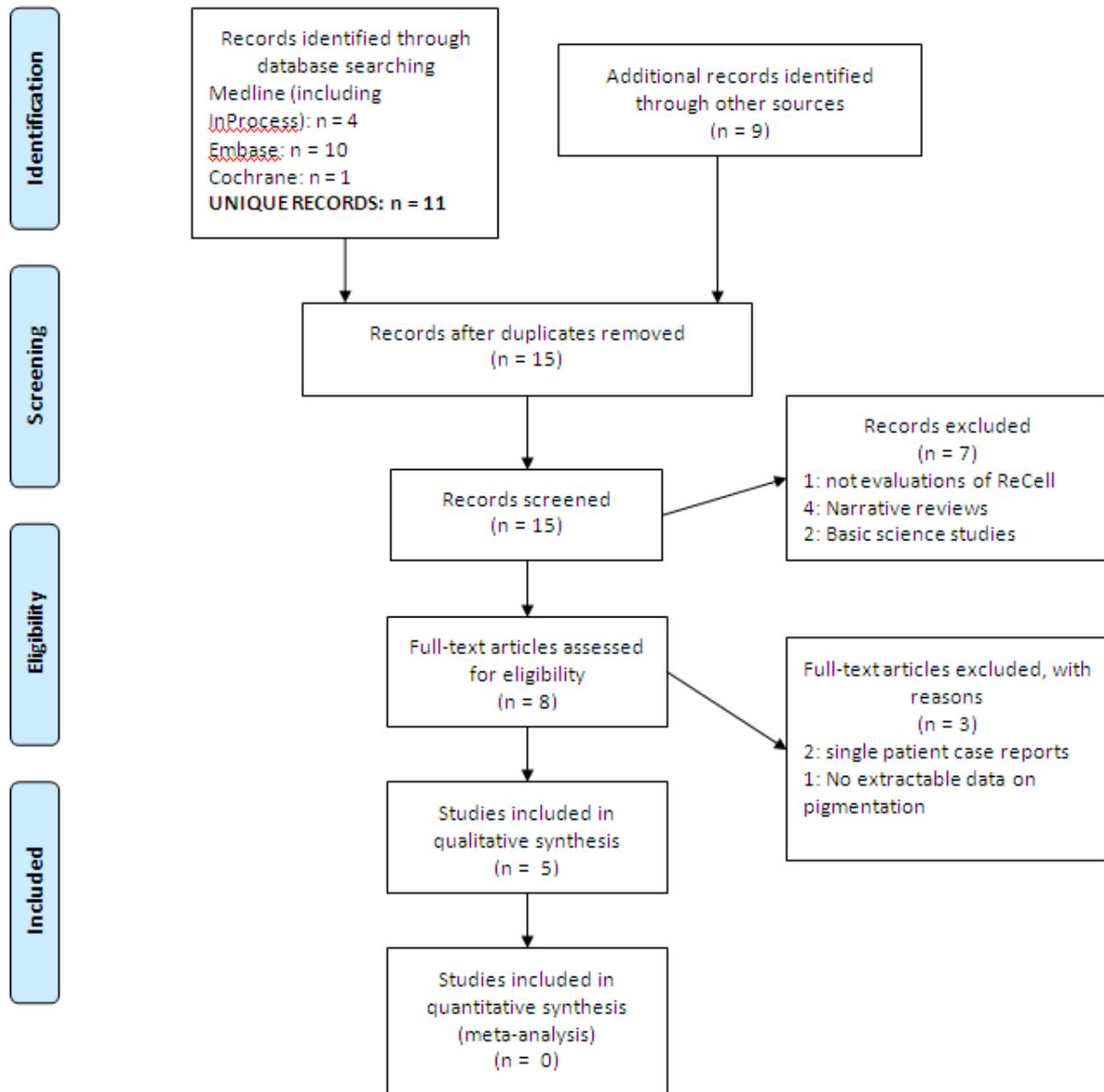


Table B2 Selection criteria used for unpublished studies

Inclusion criteria	
Population	Adults and children undergoing treatment for flame burns and scalds
Interventions	Autologous skin cell harvesting (ReCell) used either alone or in combination with other treatments
Outcomes	<ul style="list-style-type: none"> i. Speed of healing ii. Number of dressings iii. Length of stay per % TBSA iv. Wound infection rates v. Scarring: aesthetic and functional outcomes vi. Pigmentation: aesthetic and functional outcomes vii. Re-admission rates for scar management viii. Transfusion rates during skin grafting ix. Number and size of donor sites x. Growth rate in children xi. Surgical procedure and theatre time xii. Device-related adverse events xiii. Analgesic/anaesthetic use xiv. Other resource utilisation outcomes not specified above xv. Other patient-relevant outcomes not specified above
Study design	Systematic reviews with quantitative outcomes, Randomised controlled trials, non-randomised observational studies, comparative or non-comparative case series.
Language restrictions	Any language
Search dates	1995 - 2013
Exclusion criteria	
Population	Patients undergoing treatment for indications other than flame burns or scalds
Interventions	Treatments not involving autologous skin cell harvesting
Outcomes	None explicitly excluded
Study design	Narrative reviews not including direct patient effectiveness data, single patient case reports, animal studies, in vitro studies
Language restrictions	None
Search dates	Pre 1995

7.2.4 Report the numbers of unpublished studies included and excluded at each stage in an appropriate format.

One unpublished abstract of case series was identified within the main burns indication.

One unpublished manuscript of a case series was identified for the hypopigmentation subsidiary search.

7.3 Complete list of relevant studies

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

7.3.1 Provide details of all published and unpublished studies identified using the selection criteria described in tables B1 and B2.

Table B3 List of relevant published studies

Primary study reference	Study name (acronym)	Population	Intervention	Comparator
Gravante 2007 ⁷		Adults with deep partial thickness burns	ReCell	Split thickness skin graft (SSG)
Wood 2012 ⁸		Children with scalds	ReCell + Biobrane	Biobrane
Park 2013 ⁹		Patients undergoing surgery for burns	Multivariate regression analysis: Use of ReCell, SSG and SSG+ReCell explored as covariates	
Dunne 2012 ¹⁰		Children with scalds	ReCell + Biobrane	1. Biobrane 2. SSG
Rawlins 2013 ¹¹		Children with burns	ReCell	SSG
Rawlins 2011 ¹²		Adults with deep flame burns	ReCell + Biobrane	SSG
Echlin 2012a ¹³		Patients with deep partial thickness burns of face	ReCell after failed SSG	No comparator
Echlin 2012b ¹⁴		Burns patients with SSG donor sites at risk of poor healing	ReCell	No comparator
Palombo 2012 ¹⁵		Children with scarring following scalds	ReCell	No comparator
Sen 2012 ¹⁶		Patients requiring dermal grafts after initial SSG	ReCell with dermal graft	No comparator
De Angelis 2009 ¹⁷		Mixed group of patients including acute burns patients	ReCell	Unclear
Subsidiary search: hypopigmentation				
Cervelli 2009a ¹⁸		Mixed group of patients with dyspigmented or hypertrophic scars	ReCell	No comparator
Cervelli 2009b ¹⁹		Patients with stable vitiligo	ReCell	No comparator
Mulekar 2008 ²⁰		Patients with stable vitiligo	ReCell	Melanocyte-keratinocyte transplant
Daniel 2011		Patients with stable	ReCell	Minigrafting

21		vitiligo		
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*Studies identified with highlighting indicate that this paper directly relates to the comparisons defined in the decision problem.

Table B4 List of relevant unpublished studies

Data source	Study name (acronym)	Population	Intervention	Comparator
Philp 2013 abstract submitted ²²		Patients requiring dermal graft after SSG	ReCell with dermal graft	No comparator
Cui 2013 working manuscript ²³		Patients with dyspigmented scars from burns, trauma and surgery	ReCell	No comparator

7.3.2 State the rationale behind excluding any of the published studies listed in tables B3 and B4.

De Angelis 2009 ¹⁷ (table B3) was excluded on the grounds that insufficient data were available in the abstract on both methods and results to draw meaningful conclusions. Having contacted the original authors it was established that the study had never been fully published and that the data was not available to use. It was therefore decided to exclude the study.

7.4 Summary of methodology of relevant studies

7.4.1 Describe the study design and methodology for each of the published and unpublished studies using tables B5 and B6 as appropriate. A separate table should be completed for each study.

Table B5a Summary of methodology for randomised controlled trials

Study name	Gravante 2007 ⁷
Objectives	Comparison of split thickness skin grafting (SSG) with ReCell in adults with deep partial thickness burns
Location	Burns centre, S. Eugenio Hospital in Rome, Italy
Design	Randomised controlled part-blinded trial
Duration of study	Two year study with 6 months follow-up for each

	participant
Sample size	100 enrolled; 82 randomised
Inclusion criteria	Adults with deep partial thickness burns Requirement for surgical debridement and epidermal replacement Maximum burn size 320 sq cm
Exclusion criteria	Pre-existing local or systemic infection Pre-existing medical conditions that would interfere with healing: eg diabetes, malignancy, autoimmune disease Renal failure (GFR<60ml/min) Medications that would interfere with wound healing Antibiotics (non-prophylactic) for more than 48 hours prior to treatment Hypersensitivity to trypsin or Hartmann's solution High anaesthetic risk necessitating postponement of surgery
Method of randomisation	Allocated according to controlled-sampling chart to ensure homogeneity between groups for age, gender, type of burns and total bone surface area (TBSA)
Method of blinding	Part-blinded study Blinding of surgeon and patient not possible owing to distinct nature of procedures Assessment of aesthetic result carried out by independent clinician unaware of treatment allocation
Intervention(s) (n =) and comparator(s) (n =)	ReCell: n = 42 SSG: n = 40
Baseline differences	No significant differences in terms of age, gender, height, weight, burns area treated or concomitant disease prevalence
Duration of follow-up, lost to follow-up information	All patients followed up for at least six months. None lost to follow-up.
Statistical tests	Descriptive statistics for continuous quantitative variables by mean and standard deviation, following normality testing. Between-groups comparison by Student's t-testing apart from the area of skin harvested, which was compared using Mann-Whitney test, as variances were unequal. Descriptive statistics for qualitative categorical variables by frequencies, with chi-squared test and Fisher's exact test being used for comparison All p-values considered significant if <0.05
Primary outcomes (including scoring methods and timings of assessments)	a) Time for complete epithelialisation of both treated and biopsy site (days): Patients assessed by clinician at 1, 2, 3 and 4 weeks b) Aesthetic and functional quality of the epithelialisation using simplified version of the Vancouver scar scale and active and passive range of movements across relevant affected

	joints: Patients assessed at 3 and 6 months. Final measure reported.
Secondary outcomes (including scoring methods and timings of assessments)	<p>Skin area harvested (sq cm): Assessed by clinician at time of procedure</p> <p>Skin area treated (sq cm): Assessed by clinician at time of procedure</p> <p>Duration of procedure (min): Assessed by clinician at time of procedure</p> <p>Post-operative pain (visual analogue scale): Time of assessment not specified</p> <p>Adverse events (including infections/inflammation): assessed throughout follow-up period</p>

Table B5b Summary of methodology for randomised controlled trials

Study name	Wood 2012 ⁸
Objectives	Pilot study to compare Biobrane alone, Biobrane + ReCell and standard dressings in children with scald injuries
Location	Royal Perth Hospital, Perth, Australia
Design	Randomised controlled trial
Duration of study	One year study with 6 months follow-up for each participant
Sample size	13 patients
Inclusion criteria	<p>Children with scald injury</p> <p>Minimum TBSA 2%</p> <p>Anticipated not to heal spontaneously within 10 days and therefore eligible for surgery</p>
Exclusion criteria	<p>Wound not initially dressed according to protocol (Acticoat + Duoderm)</p> <p>Unsuitable for anaesthetic at 48 hours post injury</p> <p>Known contraindications, allergies or sensitivities to dressing products used in the trial</p> <p>Late presentations</p> <p>No informed consent</p> <p>Declined to participate</p>
Method of randomisation	Sealed, opaque, identical, serially numbered envelopes prepared by an independent third party
Method of blinding	No formal blinding of study. Check assessment of wound healing carried out by blinded third party. Process outcomes derived retrospectively from hospital database
Intervention(s) (n =) and comparator(s) (n =)	<p>Standard treatment: n = 4</p> <p>Biobrane alone: n = 4</p> <p>Biobrane + ReCell: n = 5</p>
Baseline differences	Generally similar. Patients in the Biobrane + ReCell

	group were younger than those in the other two groups (mean 1.3 vs 5.0). Scald size was larger in the Biobrane alone group (mean TBSA 8% vs 4.5% vs 5.2%). Small number meant that statistical significance could not be meaningfully estimated)
Duration of follow-up, lost to follow-up information	Intended follow-up was 6 months. 1 patient in the Biobrane + ReCell arm lost to follow-up after 6 weeks, so not included in long term assessments.
Statistical tests	Descriptive analyses only, owing to small sample size. Data presented as either mean + sd or median + IQR for continuous variables or number (%) for binary outcomes.
Primary outcomes (including scoring methods and timings of assessments)	Proportion of patients undergoing surgery 10 days post randomisation. Decision to operate made on clinical grounds and recorded as a binary measure (yes/no)
Secondary outcomes (including scoring methods and timings of assessments)	<p>Time to healing: number of days post-burn until dressings no longer required (clinical assessment)</p> <p>Healing rate: Digital objective wound size assessment (Visitrak) carried out at 2, 10 and 21 days post burn. Results at 10 and 21 days expressed as % healing relative to 2 day baseline reading</p> <p>Total length of hospital stay: Based on all episodes of in-patient care, including both index and re-admissions, over the 6 months following the burn</p> <p>Pain at dressing changes: assessed using age-appropriate assessment tool (CHIPPS for age < 2 years, FLACC for age 2-7, Revised Faces Pain Scale for age 8+)</p> <p>Resource utilisation: Dressing costs, analgesic costs, theatre costs, overall admission costs, scar management costs</p> <p>Long term scar outcomes assessed at 6 months using Vancouver Scar scale</p>

Table B5c Summary of methodology for randomised controlled trials

Study name	Daniel 2011 (Abstract) ²¹
Objectives	Pilot study to compare ReCell with minigrafting in patients with stable vitiligo
Location	St George Hospital, Sydney, Australia
Design	Randomised controlled trial with intra-patient controls (paired lesions in each patient randomised for treatment)
Duration of study	12 months
Sample size	14 patients (interim report)
Inclusion criteria	Not stated in abstract
Exclusion criteria	Not stated in abstract

Method of randomisation	Not stated in abstract
Method of blinding	Pre- and post-procedure photographs assessed by independent blinded investigator
Intervention(s) (n =) and comparator(s) (n =)	Intra-patient control, therefore both treatments used in all 14 patients
Baseline differences	Thanks to internal control, there should be perfect matching
Duration of follow-up, lost to follow-up information	Primary outcome assessed at 12 months. No losses to follow-up
Statistical tests	No statistical analysis given in abstract
Primary outcomes (including scoring methods and timings of assessments)	Percentage pigmentation at 12 months for each treatment. Assessed by direct measurement of photographs
Secondary outcomes (including scoring methods and timings of assessments)	Percentage pigmentation at 3 and 6 months Cosmetic outcome of donor and recipient sites, assessed by investigators and subjects

Table B6a Summary of methodology for observational studies

Study name	Park 2013 ⁹
Objective	Assess impact of skin replacement technique used on risk of infection, graft failure and length of hospital stay
Location	Royal Perth Hospital, Perth, Australia
Design	Retrospective multiple regression analysis
Duration of study	8 years
Patient population	All burns patients treated with surgical re-epithelialisation between 2004-11
Sample size	770 patients
Inclusion criteria	Patients undergoing surgical treatment for burns (SSG or other skin replacement surgery)
Exclusion criteria	Patients confirmed to have burn wound infection or community acquired infection on admission or in the pre-surgical period Admissions for subsequent surgery for reconstruction or scar revision Patients with positive sputum, urine or blood microbiology culture
Intervention(s) (n =) and comparator(s) (n =)	SSG alone: n = 387 ReCell alone: n = 73 SSG + ReCell: n = 264 Cultured epithelial cells +/- SSG: n = 46
Baseline differences	Treatment allocation reflected clinician view at the time of admission and was not randomised. However, as the primary analysis was a multiple regression, relevant

	baseline differences will have been corrected for in the results
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Hospital records (RPH Burns Minimum Dataset) accessed to ascertain details of in-hospital wound infections, graft loss and length of stay. Longer term outcomes not presented in this analysis
Statistical tests	Multivariate logistic regression analysis
Primary outcome (including scoring methods and timings of assessments)	Risk of burn wound infection, defined as the frequency of a confirmed infection in the post-surgical period that was not present prior to surgery. Diagnosis was defined by the presence of greater than 100,000 bacteria on wound swabs taken at the time of dressing change (or when indicated clinically)
Secondary outcomes	Frequency of graft loss in the post-operative period – binary assessment (yes/no) as assessed by clinician Length of hospital stay (days) for the index admission

Table B6b Summary of methodology for observational studies

Study name	Dunne 2012 (Abstract) ¹⁰
Objective	Evaluation of a dynamic treatment algorithm for paediatric scalds, escalating from Biobrane alone, to Biobrane + ReCell to early SSG according to burn depth
Location	Pinderfields General Hospital, Wakefield, UK
Design	Descriptive case series
Duration of study	18 months approx
Patient population	All paediatric scalds patients admitted to the burns unit
Sample size	40 patients
Inclusion criteria	Children with scalds, suitable for surgical management
Exclusion criteria	Injuries considered likely to heal spontaneously
Intervention(s) (n =) and comparator(s) (n =)	Superficial dermal burn: clean/debridement + Biobrane (n = 20) Mid and deep dermal burn: clean/dermabrasion + ReCell + Biobrane (n = 13) Full thickness: clean/dermabrasion + early split skin graft (n = 7)
Baseline differences	Treatments allocated according to depth of wound, therefore groups not equivalent
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of	Standard follow-up in accordance with burns centre policy and individual clinical need

follow-up, participants lost to follow-up	
Statistical tests	None
Primary outcomes (including scoring methods and timings of assessments)	Length of stay Requirement for skin grafting Long term scar assessment Speed of wound healing Donor site morbidity Analgesic requirement Dressing costs Details of scoring methods and timings not described

Table B6c Summary of methodology for observational studies

Study name	Rawlins 2013 (Abstract)¹¹
Objective	Comparison of ReCell and split-thickness skin grafts (SSG) in management of paediatric burns
Location	Pinderfields General Hospital, Wakefield, UK
Design	Descriptive case series
Duration of study	12 months
Patient population	All paediatric burns patients admitted to the burns unit requiring surgical intervention
Sample size	26 patients
Inclusion criteria	Burns requiring surgical intervention
Exclusion criteria	None described
Intervention(s) (n =) and comparator(s) (n =)	SSG: n = 15 ReCell: n = 11
Baseline differences	Patients allocated according to consultant preference. TBSA greater in the ReCell cohort compared with SSG (mean 6.5% vs 2.9%)
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Standard follow-up in accordance with burns centre policy and individual clinical need. Formal wound assessment made at 4 months post-injury
Statistical tests	None
Primary outcomes (including scoring methods and timings of assessments)	Visual analogue scale of burns healing assessed by 5 independent clinicians based on pictures taken 4 months post injury (Range: 0=normal skin – 10=poor scar) Operative time Requirement for physiotherapy

Incidence of wound infection

Table B6d Summary of methodology for observational studies

Study name	Rawlins 2011 (Abstract) ¹²
Objective	Comparison of ReCell + Biobrane and split-thickness skin grafts (SSG) for deep flame burns
Location	Pinderfields General Hospital, Wakefield, UK
Design	Descriptive case series
Duration of study	Not stated
Patient population	Patients aged 17-59 undergoing surgical treatment of deep flame burns 48-72 hours post injury
Sample size	15 patients
Inclusion criteria	Not specified
Exclusion criteria	Not specified
Intervention(s) (n =) and comparator(s) (n =)	SSG: n = 10 ReCell: n = 5
Baseline differences	Mean TBSA 15%. No differences between ReCell and SSG groups described
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Standard follow-up in accordance with burns centre policy and individual clinical need. Formal wound assessment made at 6 months post-injury
Statistical tests	None
Primary outcomes (including scoring methods and timings of assessments)	Time to wound healing Analgesia requirements Vancouver scar assessment at 6 months

Table B6e Summary of methodology for observational studies

Study name	Echlin 2012a (Abstract) ¹³
Objective	Use of ReCell on patients with deep partial thickness burns of face
Location	Chelsea & Westminster Hospital, London, UK
Design	Descriptive case series
Duration of study	Not stated
Patient population	Patients with mid to deep dermal scalds or flame burns of the whole face
Sample size	5 patients

Inclusion criteria	Patients initially treated with allograft and when assessed at 9-11 days considered unlikely to heal within 21 days
Exclusion criteria	Not specified
Intervention(s) (n =) and comparator(s) (n =)	Single arm observational series: all treated with ReCell
Baseline differences	n/a
How were participants followed-up (for example, through proactive follow-up or passively). Duration of follow-up, participants lost to follow-up	Assessed for adequacy of healing over 7 days post-operatively
Statistical tests	None
Primary outcomes (including scoring methods and timings of assessments)	Time to wound healing

Table B6f Summary of methodology for observational studies

Study name	Echlin 2012b (Abstract) ¹⁴
Objective	Use of ReCell on skin graft donor sites in burns patients
Location	Chelsea & Westminster Hospital, London, UK
Design	Descriptive case series
Duration of study	Not stated
Patient population	Patients with SSG donor sites that were either extensive or considered at risk of delayed healing
Sample size	11 sites on 9 patients
Inclusion criteria	Patients at risk of delayed healing of donor site Patients with large burns which would require multiple grafting from the same donor site
Exclusion criteria	Not specified
Intervention(s) (n =) and comparator(s) (n =)	Single arm observational series: all treated with ReCell
Baseline differences	n/a
How were participants followed-up (for example, through proactive follow-up or passively). Duration of follow-up, participants lost to follow-up	Standard care over duration of healing process up to 29 days
Statistical tests	None

Primary outcomes (including scoring methods and timings of assessments)	Time to wound healing
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Table B6g Summary of methodology for observational studies

Study name	Palombo 2012 (Abstract) ¹⁵
Objective	Use of ReCell in children with burns scarring
Location	S Eugenio Hospital, Rome, Italy
Design	Descriptive case series
Duration of study	Not stated
Patient population	Children with scarring following scalds
Sample size	6 patients
Inclusion criteria	Children with hypertrophic scarring causing aesthetic or functional problems
Exclusion criteria	Not specified
Intervention(s) (n =) and comparator(s) (n =)	Single arm observational series: all treated with ReCell
Baseline differences	n/a
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Standard follow-up over 3 months post-procedure
Statistical tests	None
Primary outcomes (including scoring methods and timings of assessments)	Time to wound healing Skin pigmentation at 3 months Scar texture at 3 months

Table B6h Summary of methodology for observational studies

Study name	Sen 2012 (Abstract) ¹⁶
Objective	Use of ReCell with split thickness dermal graft in patients with extensive burns
Location	The St. Andrew's Centre for Burns and Plastic Surgery, Chelmsford, UK
Design	Descriptive case series
Duration of study	Not stated
Patient population	Patients with extensive burns requiring dermal grafts after initial conventional SSGs

Sample size	5 patients
Inclusion criteria	Patients with burns >50% TBSA All possible donor sites already used for SSG
Exclusion criteria	Not specified
Intervention(s) (n =) and comparator(s) (n =)	Single arm observational series: split thickness dermal graft taken from base of SSG donor site. Both donor and recipient sites treated with ReCell
Baseline differences	n/a
How were participants followed-up (for example, through proactive follow-up or passively). Duration of follow-up, participants lost to follow-up	Short term report on healing
Statistical tests	None
Primary outcomes (including scoring methods and timings of assessments)	Time to wound healing assessed by two independent observers

Table B6i Summary of methodology for observational studies

Study name	Cervelli 2009a ¹⁸
Objective	Evaluation of ReCell in patients with hypopigmented post-traumatic scarring
Location	University Tot Vergata, Rome, Italy
Design	Descriptive case series
Duration of study	2 years. Minimum individual follow-up 1 year
Patient population	White adults with dyspigmented or hypertrophic scars unresponsive to previous treatments
Sample size	30 patients
Inclusion criteria	Age 20-50 White ethnicity: skin phototypes II or III Non-smoking Post traumatic scars resistant to previous treatments Affected area <320sq cm
Exclusion criteria	Presence of local or systemic infection Medical conditions or medication that could interfere with healing Use of antibiotics for >48hrs pre procedure Hypersensitivity to trypsin or Hartmann's solution High anaesthetic risk
Intervention(s) (n =) and comparator(s) (n =)	Single arm observational series: All scars treated with ReCell

Baseline differences	n/a
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Active follow-up weekly for 1 month, then at months 3,6,12 and 24. Data for all patients available to 12 months. None lost to follow-up
Statistical tests	Descriptive data only
Primary outcomes (including scoring methods and timings of assessments)	<ol style="list-style-type: none"> 1. Time for complete epithelialisation – assessed by clinician 2. Aesthetic and functional qualities of new scar – assessed by clinician, patient and family using modified Vancouver Scar scale

Table B6j Summary of methodology for observational studies

Study name	Cervelli 2009b ¹⁹
Objective	Evaluation of ReCell in patients with stable vitiligo
Location	University Tot Vergata, Rome, Italy
Design	Descriptive case series
Duration of study	1 year. Minimum individual follow-up 6 months
Patient population	Adults and adolescents with stable vitiligo
Sample size	15 patients
Inclusion criteria	Age 10+ Stable vitiligo with no progression in past year Affected area <320sq cm
Exclusion criteria	Extensive depigmentation Concomitant serious systemic disease Keloidal or bleeding tendency
Intervention(s) (n =) and comparator(s) (n =)	Single arm observational series: All patients treated with ReCell
Baseline differences	n/a
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Photographs used to document pigmentation pre-surgery and at 1, 3 and 6 months post surgery
Statistical tests	Descriptive data only
Primary outcomes (including scoring)	<ol style="list-style-type: none"> 1. Repigmentation assessed using visual analogue scale and 6-point ordinal global assessment.

methods and timings of assessments)	Both assessments carried out by both clinician and patient 2. Overall cosmetic result using four point ordinal scale carried out by clinician, patient, family members and close friends
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Table B6k Summary of methodology for observational studies

Study name	Mulekar 2008 ²⁰
Objective	Evaluation of ReCell in patients with stable vitiligo
Location	National Centre for Vitiligo and Psoriasis, Riyadh, Saudi Arabia
Design	Comparative case series
Duration of study	4 months
Patient population	Adults with stable vitiligo
Sample size	5 patients
Inclusion criteria	Patients with stable vitiligo At least two lesions in the same anatomical location
Exclusion criteria	None specified
Intervention(s) (n =) and comparator(s) (n =)	Internally controlled by paired lesions: All patients (n=5) treated with both ReCell and melanocyte-keratinocyte transplantation
Baseline differences	None
How were participants followed-up (for example, through proactive follow-up or passively). Duration of follow-up, participants lost to follow-up	All patients attended for lesion photography at baseline and 4 months. No losses to follow-up
Statistical tests	Descriptive data only
Primary outcomes (including scoring methods and timings of assessments)	Percentage area of repigmentation in test lesions at four months compared to pre-surgery. Assessed using direct measurement of photographs by two independent clinicians.

Table B6l Summary of methodology for observational studies

Study name	Cui 2013 (Draft manuscript) ²³
Objective	Evaluation of ReCell in patients with dyspigmented scars
Location	Peking Union Medical College Hospital, Beijing, China

Design	Descriptive case series
Duration of study	12 months
Patient population	Adults and adolescents with dyspigmented scars due to injury, disease or surgery
Sample size	12 patients (9 following burns)
Inclusion criteria	Age 15-50 Chinese Non-smoking Dyspigmented scar Affected area <320sq cm
Exclusion criteria	Presence of local or systemic infection Medical conditions or medication that could interfere with healing Use of antibiotics for >48hrs pre procedure Hypersensitivity to trypsin or Hartmann's solution High anaesthetic risk
Intervention(s) (n =) and comparator(s) (n =)	No comparative: all patients received ReCell
Baseline differences	n/a
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Active follow-up weekly for 1 month, then at months 3,6 and 12. Photographs taken at each visit. Data for all patients available to 12 months. None lost to follow-up
Statistical tests	Descriptive data only
Primary outcomes (including scoring methods and timings of assessments)	Qualitative assessment of pigmentation assessed at 12 months using modified Vancouver Scar Scale. Assessment carried out by both patient and clinician

Table B6m Summary of methodology for observational studies

Study name	Philp 2013 (Submitted abstract) ²²
Objective	Use of ReCell with split thickness dermal graft in patients with extensive burns
Location	The St. Andrew's Centre for Burns and Plastic Surgery, Chelmsford, UK
Design	Descriptive case series
Duration of study	Not stated
Patient population	Patients requiring dermal grafts after initial conventional SSGs
Sample size	10 patients
Inclusion criteria	Not specified

Exclusion criteria	Not specified
Intervention(s) (n =) and comparator(s) (n =)	Single arm observational series: split thickness dermal graft taken from base of SSG donor site. Both donor and recipient sites treated with ReCell. Recipient site dressed with Biobrane or Telfa
Baseline differences	n/a
How were participants followed-up (for example, through proactive follow-up or passively). Duration of follow-up, participants lost to follow-up	Graft sites inspected every 2 days until healed. Otherwise standard of care
Statistical tests	None
Primary outcomes (including scoring methods and timings of assessments)	Time to healing at graft site Time to healing at donor site Long term scar assessment

7.4.2 Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).

Philp 2013²² reports on 10 patients undergoing dermal grafting. These patients include the five for whom preliminary data were reported in Sen 2012¹⁶, in addition to five new patients.

7.4.3 Highlight any differences between patient populations and methodology in all included studies.

There are significant differences in baseline characteristics of patients included in the identified studies. This reflects that the studies are small and the samples described are drawn from an extremely heterogeneous population. Outcomes in burns patients are very susceptible to individual factors, such as age, extent, depth and location of burns and the presence of co-morbidities or adverse social circumstances. Thus, within the studies identified, age ranges from 9 months (Dunne 2012a¹⁰) to 80 years (Echlin 2012b¹⁴). TBSA ranged from <2% (Gravante 2007⁷) to >50% (Sen 2012¹⁶).

This degree of between-studies variation precludes meta-analysis and makes qualitative generalisation of results difficult to achieve. In some ways, however, this is less of a disadvantage than might be the case in some other disease areas. Burns management is highly individualised – as highlighted by the lack of published clinical guidelines and its exclusion from the Payment by Results tariff. This means that the use of ReCell will always be tailored to the clinical circumstances of the individual patient, rather than based on any population-level estimates of efficacy.

7.4.4 Provide details of any subgroup analyses that were undertaken in the studies included in section 7.4.1. Specify the rationale and state whether these analyses were pre-planned or post-hoc.

No sub-group analyses described

7.4.5 If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment in an appropriate format.

CONSORT diagrams below for the two published randomised controlled trials (Gravante 2007 ⁷ and Wood 2012 ⁸). Insufficient data are available from the abstract of the third RCT (Daniel 2011) ²¹ to provide these details.

Figure 3: CONSORT diagram for Gravante 2007 ⁷

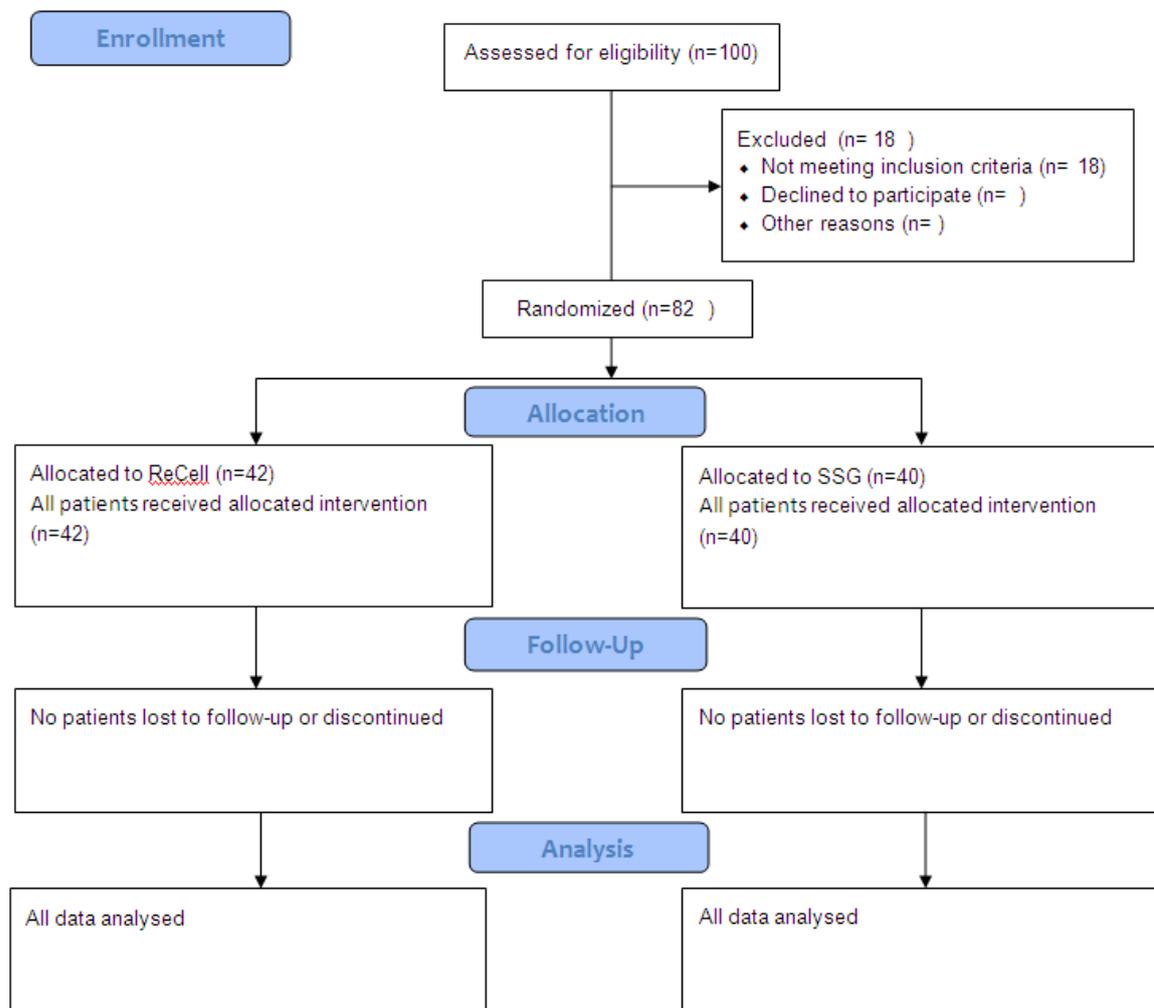
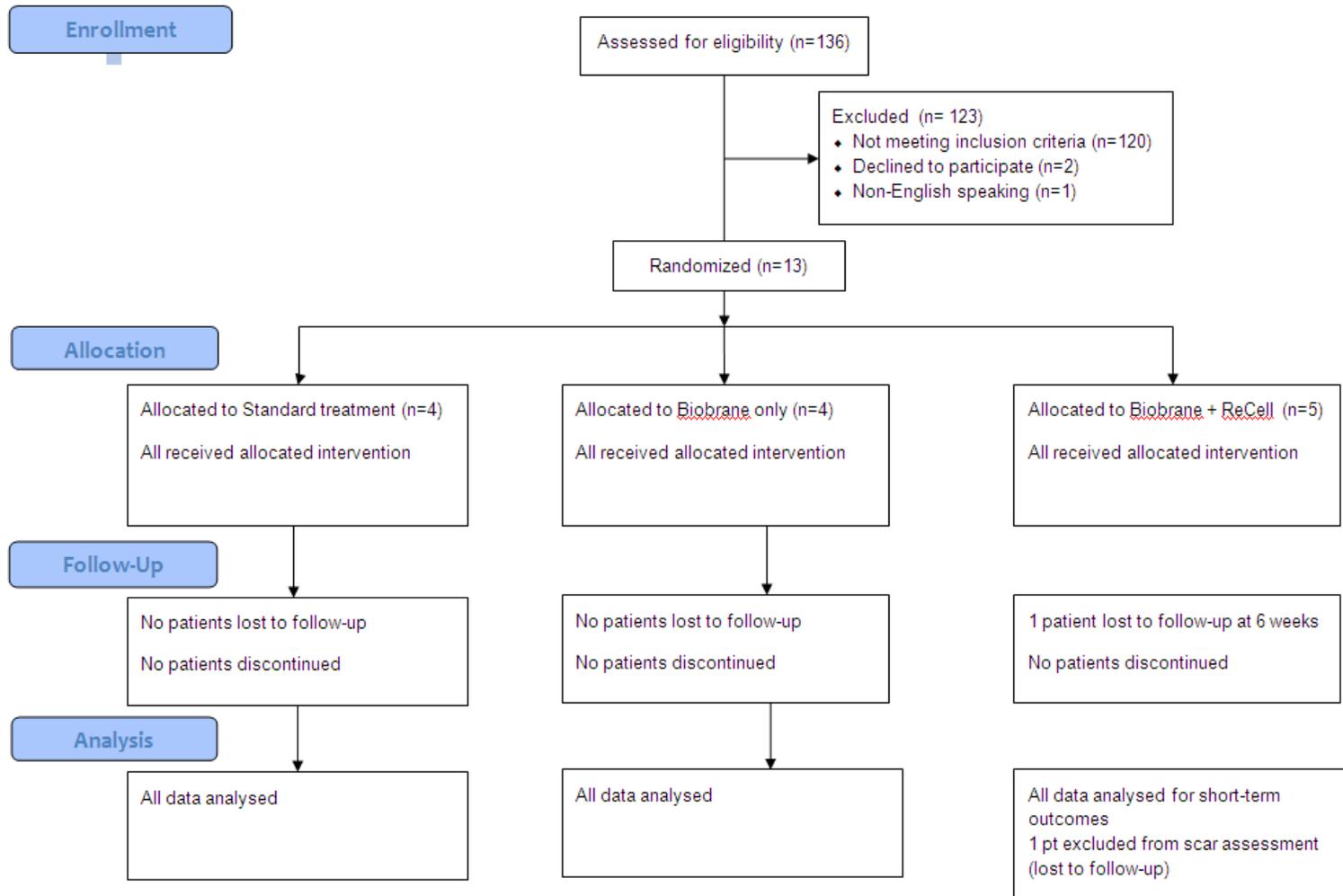


Figure 4: CONSORT diagram for Wood 2011 ⁸



7.4.6 If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.

One patient in the Biobrane + ReCell arm of Wood 2012⁸ was lost to follow-up at six weeks post randomisation. No further details are given in the paper. All data for the in-hospital outcomes were included in the analysis for this patient, but they were excluded from the long term scar outcome analysis, as they did not attend for this assessment.

7.5 **Critical appraisal of relevant studies**

7.5.1 Complete a separate quality assessment table for each study. A suggested format for the quality assessment results is shown in tables B7 and B8.

Table B7a Critical appraisal of randomised control trials

Study name	Gravante 2007 ⁷	
Study question	Response (yes/no/not clear/N/A)	How is the question addressed in the study?
Was randomisation carried out appropriately?	Not clear	The authors describe a process of controlled sampling to match patient groups but it is not clear whether this was a randomised process
Was the concealment of treatment allocation adequate?	Not clear	
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Relatively tight inclusion/exclusion criteria + between groups matching for age, gender, type of burns and TBSA ensure good comparability
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of	Care providers: No Patients: No Assessors: Mixed	The differing nature of the two interventions made blinding of patients and assessors impossible. However, as the short term outcomes assessed were largely numerical and objective (healing time, operative duration, area treated) this should not have introduced bias. One subjective measure (post operative pain) may have been open to bias due to lack of patient blinding. Long term assessment of scar quality was

bias (for each outcome)?		carried out by one unblinded and one blinded assessor, while functional status was assessed by a physical therapist whose blinding status is unknown. Thus there has been an attempt to mitigate the effect of lack of blinding but it is unclear to what extent this has been achieved
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	No dropouts reported
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	As all patients randomised received their allocated treatment and there were no dropouts, the data presented represent the ITT population
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Table B7b Critical appraisal of randomised control trials

Study name	Wood 2012⁸	
Study question	Response (yes/no/not clear/N/A)	How is the question addressed in the study?
Was randomisation carried out appropriately?	Yes	Sealed, opaque, identical, serially numbered envelopes prepared by a third party
Was the concealment of treatment allocation adequate?	Yes	
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	No	Given the small patient numbers recruited, between-groups differences were inevitable. Most marked difference is in age, with Biobrane + ReCell patients being markedly younger than the other two groups

Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Care providers: No Patients: No Assessors: Mixed	As for the previous study, the differing nature of the two interventions made blinding of patients and assessors impossible. Some of the outcome were numerical and objective (Requirement for surgery, healing time, number of dressing changes) and therefore resistant to the effect of bias. One subjective measure (post operative pain) may have been open to bias thanks to lack of patient blinding. Assessment of healing was validated by a blinded independent assessor using photographs
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	Only one dropout in the Biobrane + ReCell group
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	All data available were presented, which was effectively an ITT analysis for all except the final scar assessment, which excluded the missing patient. However, as the number of patients were so small, no attempt at statistical analysis was made, so the distinction of ITT vs PP is probably moot.
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Table B7c Critical appraisal of randomised control trials

Study name	Daniel 2011 (abstract)²¹	
Study question	Response (yes/no/not clear/N/A)	How is the question addressed in the study?
Was randomisation carried out appropriately?	Not clear	
Was the concealment of treatment allocation	Yes	All patients treated with both interventions, hence treatment allocation inherently unbiased

adequate?		
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Intra-patient control, hence matching will be perfect
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Care providers: No Patients: No Assessors: Yes	The differing nature of the interventions makes blinding of patients and clinicians impractical. Assessment of outcomes carried out by independent blinded assessor
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	All patients followed up. Internal control means that balance will be inherently maintained in the event of drop-outs
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	n/a	Interim report only – formal analysis not presented at this stage
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Table B8 Critical appraisal of observational studies

Study name Park 2013 ⁹		
Study question	Response yes/no/not clear/N/A)	How is the question addressed in the study?
Was the cohort	Yes	All patients undergoing surgery for burns in a

recruited in an acceptable way?		large regional burns unit over an 8 year period were included
Was the exposure accurately measured to minimise bias?	Yes	Source of data was a dedicated burns dataset on which detailed records had been entered at the time of the original admission. Variables used in the analysis were derived from this and not subject to retrospective alteration
Was the outcome accurately measured to minimise bias?	Yes	Of the three outcomes assessed, two (wound infection and length of stay) were explicitly defined and recorded at the time of admission. The third outcome (graft loss) was a clinical opinion and therefore potentially prone to bias, but the data was recorded at the time of the original admission and not retrospectively altered
Have the authors identified all important confounding factors?	Unclear	The authors identified a number of factors that were thought likely to influence the outcomes of interest. It is possible that other confounders exist that were not recorded in the dataset that forms the basis of this analysis
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Univariate analysis was first carried out for each of the potential confounders, in order to identify the covariates that should be included in the multivariate logistic regression analysis
Was the follow-up of patients complete?	Yes	48 patients were excluded from the analysis, on grounds of pre-existing signs of wound or systemic infection. All other patients are included in the analysis
How precise (for example, in terms of confidence interval and p values) are the results?		Results for each variable in each of the three regression analyses are presented as odds ratio, 95% CI and p-value. All figures are quoted to two decimal places
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

As all the other published observational studies identified were simple case series, methodological critical appraisal is inappropriate and data are therefore not presented here.

7.6 Results of the relevant studies

7.6.1 Complete a results table for each study with all relevant outcome measures pertinent to the decision problem. A suggested format is given in table B9.

Table B9a Outcomes from published and unpublished studies – results reported for primary outcomes and secondary outcomes relevant to decision problem

Study name		Gravante 2007 ⁷
Size of study groups	Treatment	42
	Control	40
		Formal sample size estimation not defined in paper
Study duration	Time unit	2 years total. 6 months follow-up for each individual
Type of analysis	Intention-to-treat/per protocol	Intention to treat
Primary Outcome	Name	Time for complete epithelialisation
	Unit	Days
Effect size	Value	Mean 13 days in ReCell group (sd = 2) Mean 12 days in SSG group (sd = 2) Mean difference = 1 day
	95% CI	Not specified in paper. Our estimated confidence interval for the mean difference, based on the provided data is 0.12 – 1.88
Statistical test	Type	Student's t-test
	p value	Not significant
Second primary outcome	Name	Aesthetic result
	Unit	Score on modified Vancouver Scar Scale (ordinal value between 0-5)
Effect size	Value	Values not reported in paper
	95% CI	
Statistical test	Type	Chi squared test
	p value	Reported as no significant difference
Other outcome	Name	Area harvested
	Unit	Sq cm
Effect size	Value	Mean 2.2 in ReCell group (sd = 1) Mean 110 in SSG group (sd = 50) Mean difference = 107.8 sq cm
	95% CI	Not specified in paper. Our estimated confidence interval for the mean difference, based on the provided data is 92 – 123

Statistical test	Type	Student's t-test
	p value	<0.001
Other outcome	Name	Procedure duration
	Unit	minutes
Effect size	Value	Mean 59 in ReCell group (sd = 4) Mean 20 in SSG group (sd = 6) Mean difference = 39 minutes
	95% CI	Not specified in paper. Our estimated confidence interval for the mean difference, based on the provided data is 36.8 – 41.2
Statistical test	Type	Student's t-test
	p value	<0.001
Other outcome	Name	Post-operative pain
	Unit	Visual analogue scale (range 0-10; high = worse)
Effect size	Value	Mean 3.3 in ReCell group (sd = 1.6) Mean 6.8 in SSG group (sd = 1.2) Mean difference = 3.5
	95% CI	Not specified in paper. Our estimated confidence interval for the mean difference, based on the provided data is 2.9 – 4.1.
Statistical test	Type	Student's t-test
	p value	0.03

Table B9b Outcomes from published and unpublished studies – results reported for primary outcome and secondary outcomes relevant to decision problem

Study name		Wood 2012⁸
Size of study groups	Treatment	5 (Biobrane + ReCell)
	Control	4 (Biobrane alone)
		4 (Standard treatment)
Sample size		Sample size was calculated as 45 patients, based on the expected incidence of qualifying childhood scalds over the planned 12 month duration of the study. Reductions in the expected incidence and extent of presenting scalds meant that only 16 qualifying patients could be identified, of which 13 were randomised
Study duration	Time unit	1 year total. 6 months follow-up for each individual
Type of analysis	Intention-to-treat/per protocol	Intention to treat for primary outcome and most secondary outcomes. Loss of one child to follow-up meant that the final scar assessment was effectively a per protocol analysis
Primary outcome	Name	Requirement for surgery after 10 days
	Unit	Number of patients
Effect size	Value	3 / 4 patients in standard treatment arm 1 / 4 in Biobrane only arm 0 / 5 in Biobrane + ReCell arm
	95% CI	Small numbers recruited meant that statistical analysis would have been of doubtful validity. Consequently, only descriptive data are presented.
Statistical test	Type	
	p value	
Other outcome	Name	Time to healing
	Unit	Clinician assessment of first day on which full healing was observed Quantitative assessment of unhealed wound size using Visitrak compared at 10 and 21 days versus baseline assessment at 2 days (% healed)
Effect size	Value	Standard treatment arm. <ul style="list-style-type: none"> • Mean time to heal: 34.25 days (sd 14.39) • Median time to heal: 36.5 days (IQR 18.5-47.7) • % healed at 10 days: 71.2% • % healed at 21 days: 90.1% Biobrane alone treatment arm. <ul style="list-style-type: none"> • Mean time to heal: 17.75 days (sd 4.99) • Median time to heal: 16.0 days (IQR 14.25-23.0) • % healed at 10 days: 83.2% • % healed at 21 days: 97.7%

		Biobrane + ReCell treatment arm. <ul style="list-style-type: none"> • Mean time to heal: 15 days (sd 3.54) • Median time to heal: 16 days (IQR 11.5-18) • % healed at 10 days: 95% • % healed at 21 days: 100%
	95% CI	Small numbers recruited meant that statistical analysis would have been of doubtful validity. Consequently, only descriptive data are presented
Statistical test	Type	
	p value	
Other outcome	Name	Dressing changes
	Unit	Number over course of treatment until wound healed
Effect size	Value	Standard treatment arm. <ul style="list-style-type: none"> • Mean dressing changes: 11.5 (sd 4.79) • Median dressing changes: 12.5 (IQR 8-15) Biobrane alone treatment arm. <ul style="list-style-type: none"> • Mean dressing changes: 7.5 (sd 2.64) • Median dressing changes: 7 (IQR 5.5-9.5) Biobrane + ReCell treatment arm. <ul style="list-style-type: none"> • Mean dressing changes: 4.8 (sd 1.30) • Median dressing changes: 5 (IQR 4-6)
	95% CI	Small numbers recruited meant that statistical analysis would have been of doubtful validity. Consequently, only descriptive data are presented
Statistical test	Type	
	p value	
Other outcome	Name	Pain assessment
	Unit	Numerical score from one of three age-appropriate pain assessment tools
Effect size	Value	Standard treatment arm. <ul style="list-style-type: none"> • Median pre-op score: 4.5 • Median post-op score: 5.5 • Median difference: +1.0 Biobrane alone treatment arm. <ul style="list-style-type: none"> • Median pre-op score: 4.0 • Median post-op score: 2.0 • Median difference: -2.0 Biobrane + ReCell treatment arm. <ul style="list-style-type: none"> • Median pre-op score: 4.0 • Median post-op score: 3.0 • Median difference: -1.0
	95% CI	Small numbers recruited meant that statistical analysis would have been of doubtful validity.
Statistical	Type	

test	p value	Consequently, only descriptive data are presented
Other outcome	Name	Scar outcomes
	Unit	Vancouver Scar Scale: a four item assessment yielding an ordinal value in the range 0-13 (high = worse)
Effect size	Value	Standard treatment arm. <ul style="list-style-type: none"> • Scores: 0, 6, 5, 6 Biobrane alone treatment arm. <ul style="list-style-type: none"> • Scores: 3, 9, 3, 2 Biobrane + ReCell treatment arm. <ul style="list-style-type: none"> • Scores: 5, 3, 0, 6 (+ 1 lost to follow-up)
	95% CI	Small numbers recruited meant that statistical analysis would have been of doubtful validity.
Statistical test	Type	Consequently, only descriptive data are presented
	p value	

Table B9c Outcomes from published and unpublished studies – results reported for primary outcome and secondary outcomes relevant to decision problem

Study name		Daniel 2011 (Abstract) ²¹
Size of study groups	ReCell	14 patients with intra-patient control – all received both treatments
	Minigrafting	
Study duration	Time unit	12 months
Type of analysis	Intention-to-treat/per protocol	ITT – data from all patients presented
Primary Outcome	Name	Percentage repigmentation at 12 months
	Unit	%
Effect size	Value	ReCell: 15% Minigrafting: 12%
	95% CI	Interim report: descriptive data only
Statistical test	Type	
	p value	
Secondary outcome	Name	Percentage repigmentation at 3 months
	Unit	%
Effect size	Value	ReCell: 27% Minigrafting: 11%
	95% CI	Interim report: descriptive data only
Statistical test	Type	
	p value	

Table B9d Outcomes from published and unpublished studies – results reported for primary outcome and secondary outcomes relevant to decision problem

Study name		Park 2013 ⁹
Size of study groups	ReCell alone	73
	ReCell + SSG	264
	SSG alone	387
	Cell culture +/- SSG	46 (this category relates to a cell culture technology that is no longer available, so data relating to this group are not presented below)
Study duration	Time unit	8 years total. Each individual followed up until discharge
Type of analysis	Intention-to-treat/per protocol	Not relevant to retrospective regression analysis
Primary Outcome	Name	Frequency of new burn wound infection
	Unit	Hazard ratio for infection associated with each surgery type vs SSG alone (reference) in multivariate logistic regression analysis
Effect size	Value	SSG alone: 1.00 ReCell alone: 0.78 ReCell + SSG: 1.23
	95% CI	ReCell alone: 0.34 – 3.42 ReCell + SSG: 0.45 – 4.52
Statistical test	Type	Not specified
	p value	ReCell alone: 0.98 ReCell + SSG: 0.97
Second primary outcome	Name	Frequency of graft loss
	Unit	Hazard ratio for graft loss associated with each surgery type vs SSG alone (reference) in multivariate logistic regression analysis
Effect size	Value	SSG alone: 1.00 ReCell alone: 0.89 ReCell + SSG: 1.56
	95% CI	ReCell alone: 0.45 – 2.32 ReCell + SSG: 0.56 – 3.21
Statistical test	Type	Not specified
	p value	ReCell alone: 0.09 ReCell + SSG: 0.67

Other outcome	Name	Length of stay
	Unit	Hazard ratio for increased length of stay associated with each surgery type vs SSG alone (reference) in multivariate logistic regression analysis
Effect size	Value	SSG alone: 1.00 ReCell alone: 0.70 ReCell + SSG: 0.98
	95% CI	ReCell alone: 0.57 – 0.82 ReCell + SSG: 0.88 – 1.10

Table B9e Outcomes from published and unpublished studies – results reported for primary outcome and secondary outcomes relevant to decision problem

Study name		Dunne 2012 (Abstract) ¹⁰
Size of study groups	ReCell + Biobrane	13
	Biobrane alone	20
	Early SSG	7
Study duration	Time unit	18 months approx
Type of analysis	Intention-to-treat/per protocol	Not relevant: descriptive case series
Outcome	Name	Requirement for skin grafting
	Unit	N (%)
Effect size	Value	ReCell + Biobrane: 5 (38%) Biobrane alone: 6 (30%) Early SSG: 2 (29%)
	95% CI	Descriptive data only
Statistical test	Type	
	p value	
	Minigrafting	
Statistical test	Type	
	p value	

Table B9f Outcomes from published and unpublished studies – results reported for primary outcome and secondary outcomes relevant to decision problem

Study name		Rawlins 2013 (Abstract) ¹¹
Size of study groups	ReCell	11
	SSG	15
Study duration	Time unit	4 months
Type of analysis	Intention-to-treat/per protocol	Not relevant: descriptive case series
Outcome	Name	Scar outcome
	Unit	VAS (mean)
Effect size	Value	ReCell: 3.9 SSG: 3.9
	95% CI	ReCell: 2.8 – 4.9 SSG: 3.3 – 4.5
Statistical test	Type	Not stated
	p value	P=0.97
Outcome	Name	Operative time
	Unit	Minutes
Effect size	Value	ReCell: 87 mins SSG: 58 mins
	95% CI	Not stated
Statistical test	Type	Not stated
	P value	P=0.05
Outcome	Name	Mean duration of physio follow-up
	Unit	Days
Effect size	Value	ReCell: 21 days SSG: 40 days
	95% CI	Not stated
Statistical test	Type	Not stated
	P value	P=0.29

Table B9g Outcomes from published and unpublished studies – results reported for primary outcome and secondary outcomes relevant to decision problem

Study name		Rawlins 2011 (Abstract) ¹²
Size of study groups	ReCell + Biobrane	5
	SSG	10
Study duration	Time unit	4 months
Type of analysis	Intention-to-treat/per protocol	Not relevant: descriptive case series
Outcome	Name	Mean time to wound healing
	Unit	Days
Effect size	Value	ReCell: 18 days SSG: 48 days
	95% CI	Not stated
Statistical test	Type	Not stated
	p value	Not stated

Table B9h Outcomes from published and unpublished studies – results reported for primary outcome and secondary outcomes relevant to decision problem

Study name		Echlin 2012a (Abstract) ¹³
Size of study groups	ReCell	5
Study duration	Time unit	Not specified
Type of analysis	Intention-to-treat/per protocol	Not relevant: descriptive case series
Outcome	Name	Mean time to wound healing
	Unit	Days
Effect size	Value	ReCell: 5 days
	95% CI	Not stated
Statistical test	Type	Not relevant
	p value	Not relevant

Table B9i Outcomes from published and unpublished studies – results reported for primary outcome and secondary outcomes relevant to decision problem

Study name		Echlin 2012b (Abstract) ¹⁴
Size of study groups	ReCell	11 sites in 9 patients
Study duration	Time unit	Not specified
Type of analysis	Intention-to-treat/per protocol	Not relevant: descriptive case series
Outcome	Name	Mean time to wound healing (donor site)
	Unit	Days
Effect size	Value	ReCell: 9 days
	95% CI	Not stated
	Type	Not relevant
Statistical test	p value	Not relevant

Table B9j Outcomes from published and unpublished studies – results reported for primary outcome and secondary outcomes relevant to decision problem

Study name		Palombo 2012 (Abstract) ¹⁵
Size of study groups	ReCell	6 patients
Study duration	Time unit	Not specified
Type of analysis	Intention-to-treat/per protocol	Not relevant: descriptive case series
Outcome	Name	Time to complete re-epithelialisation
	Unit	Days
Effect size	Value	ReCell: All patients healed by 10 days
	95% CI	Not stated
	Type	Not relevant
Statistical test	p value	Not relevant

Table B9k Outcomes from published and unpublished studies – results reported for primary outcome and secondary outcomes relevant to decision problem

Study name		Sen 2012 (Abstract) ¹⁶
Size of study groups	ReCell	5 patients
Study duration	Time unit	Not specified
Type of analysis	Intention-to-treat/per protocol	Not relevant: descriptive case series
Outcome	Name	Time to healing
	Unit	Not specified
Effect size	Value	ReCell: “Epithelialisation appeared complete in all cases and in times comparable to conventional graft and donor site healing”
Statistical test	95% CI	Not stated
	Type	Not relevant
	p value	Not relevant

Table B9l Outcomes from published and unpublished studies – results reported for primary outcome and secondary outcomes relevant to decision problem

Study name		Philp 2013 (Submitted abstract) ²² NOTE: Extended data relating to previous abstract (Sen 2012 ¹⁶)
Size of study groups	ReCell	10 patients (2 died – results for 8 survivors presented)
Study duration	Time unit	Not specified
Type of analysis	Intention-to-treat/per protocol	Not relevant: descriptive case series
Outcome	Name	Time to healing
	Unit	Days
Effect size	Value	ReCell: 12 days (graft) 14 days (donor)
Statistical test	95% CI	Not stated
	Type	Not relevant
	p value	Not relevant

Table B9m Outcomes from published and unpublished studies – results reported for primary outcome and secondary outcomes relevant to decision problem

Study name		Cervelli 2009a ¹⁸
Size of study groups	ReCell	30 patients
Study duration	Time unit	2 years (minimum follow up 1 year)
Type of analysis	Intention-to-treat/per protocol	Not relevant: descriptive case series
Outcome	Name	Patient assessment of outcome
	Unit	Categorical N (%)
Effect size	Value	Excellent: 18 (60%) Good: 8 (27%) Fair: 1 (3%) Poor: 3 (10%)
	95% CI	Not stated
Statistical test	Type	Not relevant
	p value	Not relevant
Outcome	Name	Surgeon assessment of outcome
	Unit	Categorical N (%)
Effect size	Value	Excellent: 18 (60%) Good: 6 (20%) Fair: 3 (10%) Poor: 3 (10%)
	95% CI	Not stated
Statistical test	Type	Not relevant
	P value	Not relevant
Outcome	Name	Pigmentation grading
	Unit	Categorical N (%)
Effect size	Value	Normal: 18 (60%) Slight: 9 (30%) Moderate: 3 (10%)
	95% CI	Not stated
Statistical test	Type	Not relevant
	P value	Not relevant

Table B9n Outcomes from published and unpublished studies – results reported for primary outcome and secondary outcomes relevant to decision problem

Study name		Cervelli 2009b ¹⁹
Size of study groups	ReCell	15 patients
Study duration	Time unit	1 years (minimum follow up 6 months)
Type of analysis	Intention-to-treat/per protocol	Not relevant: descriptive case series
Outcome	Name	Extent of pigmentation
	Unit	Ordinal N (%)
Effect size	Value	100%: 0 (0%) 76-99%: 12 (80%) 51-75%: 0 (0%) 25-50%: 3 (20%) 1-25%: 0 (0%)
	95% CI	Not stated
	Type	Not relevant
	p value	Not relevant
Statistical test		
Outcome	Name	Patient assessment of outcome
	Unit	Categorical N (%)
Effect size	Value	Excellent: 10 (67%) Good: 5 (33%) Fair: 0 (0%) Poor: 0 (0%)
	95% CI	Not stated
Statistical test	Type	Not relevant
	P value	Not relevant

Table B9o Outcomes from published and unpublished studies – results reported for primary outcome and secondary outcomes relevant to decision problem

Study name		Mulekar 2008 ²⁰
Size of study groups	ReCell	5 patients with intra-patient controls so all patients received both treatments
	M-K transplant	
Study duration	Time unit	4 months
Type of analysis	Intention-to-treat/per protocol	Not relevant: descriptive comparative case series
Outcome	Name	Percentage repigmentation at 4 months
	Unit	%
Effect size Statistical test	Value	Pt 1: ReCell – 100%; MKT – 100% Pt 1: ReCell – 40%; MKT – 30% Pt 1: ReCell – 0%; MKT – 0% Pt 1: ReCell – 65%; MKT – 100% Pt 1: ReCell – 100%; MKT – 100%
	95% CI	Not stated
	Type	Not relevant
	p value	Not relevant

7.7.1 Using the previous instructions in sections 7.1 to 7.6, provide details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results.

The original literature search described in section 7.1 above also captured studies reporting adverse events. The following studies specifically reported adverse event rates:

Gravante 2007 ⁷; Wood 2012 ⁸; Park 2013 ⁹; Rawlins 2013 ¹¹

7.7.2 Provide details of all important adverse events reported for each study. A suggested format is shown in table B10.

Because the majority of the data relating to ReCell are derived from observational studies that did not collect adverse event data using formal MedDRA criteria, these results are presented in narrative format in the table below:

Table B10 Adverse events described in studies

Study	Populations						Events		
	Treatment 1		Treatment 2		Treatment 3		Treatment 1	Treatment 2	Treatment 3
	Type	N	Type	N	Type	N			
Gravante 2007 ⁷	ReCell	42	SSG	44			No intra-operative or post-operative events reported	No intra-operative or post-operative events reported	
Wood 2012 ⁸	Conventional	4	Biobrane	4	Biobrane + ReCell	5	1 graft loss (25%) + 1 overgranulation (25%)	1 wound infection (25%)	1 wound infection (20%) + 1 sepsis (20%) [same patient]
Park 2013 ⁹	SSG	387	ReCell	73	SSG + ReCell	264	91 patients (11.8%) had a new wound infection. No significant difference between groups (SSG: HR=1.00, ReCell: HR=0.78, SSG+ReCell: HR=1.32) 116 patients (15.1%) experienced graft loss. No significant difference between groups (SSG: HR=1.00, ReCell: HR=0.89, SSG+ReCell: HR=1.56)		
Rawlins 2013 ¹¹	ReCell	11	SSG	15			2 wound infections (18%)	2 wound infections (13%)	

7.7.3 Describe all adverse events and outcomes associated with the technology in national regulatory databases such as those maintained by the MHRA and FDA (Maude).

In accordance with European regulations, any event which meets all three basic reporting criteria listed below is considered an incident and is reported to the relevant National Competent Authority by Avita Medical Ltd:

1. *An event has occurred such as:*
 - *A malfunction or deterioration in the characteristics or performance (failure to perform in accordance with intended use, when used in accordance with the instructions for use)*
 - *Unanticipated adverse reaction or unanticipated side effect*
 - *Degradation/destruction of the device (i.e. fire)*
 - *Inaccuracy of the labelling, instructions for use or promotional materials*
2. *Avita Medical's device is suspected to be a contributory cause of the incident*
3. *The event led, or might have led to the following:*
 - *Death of a patient, user or other person*
 - *Serious deterioration in the state of health of a patient, user or other person*

No such event has been reported since ReCell has been granted CE recognition (March 2005) and so there are no data to list in this paragraph

7.7.4 Provide a brief overview of the safety of the technology in relation to the scope.

The ReCell device itself is associated with an inherently low risk of adverse events, as the device itself at no point comes into contact with the patient. Trypsin and sodium lactate are used in the processing of the patient's own cells, which are then re-applied to the patient's wound. Although, in theory, sensitivity or allergy to either of these two components could result in an adverse event, in clinical practice this has never been reported.

Adverse events reported within clinical trials and observational studies tend therefore to be related to the surgical procedure and the immediate post-operative management process. The most important of these are wound infections, sepsis and graft loss – events that are familiar complications of burns management and which are associated with established mechanisms for identification and treatment.

The retrospective analysis of 770 patients treated with various surgical interventions at a single burns unit in Australia carried out by Park et al⁹ offers the best perspective on the relative risk of these adverse events with a range of treatment modalities. In this series, 50.3% of patients were treated with SSG, 9.5% with ReCell alone and 43.3% with SSG and ReCell combined. 11.8% of patients had microbiologically proven wound infections and 15.1% experienced graft loss (not mutually exclusive). After correcting for age, type and extent of injury and co-morbid diabetes, there was no significant effect of intervention type on the risk of either outcome (see table B9c).

Studies carried out in other indications for ReCell (principally vitiligo and venous leg ulcers) have not demonstrated any other adverse event signal not demonstrated in these burns studies.

These data, combined with the lack of reportable adverse events reported from clinical practice, offer strong reassurance that the use of ReCell is not currently associated with any significant risk of device-related adverse events, nor with an increase in the expected level of procedure-related complications.

7.8 Evidence synthesis and meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be considered.

Section 7.8 should be read in conjunction with the 'Medical Technologies Evaluation Programme Methods Guide', available from www.nice.org.uk/mt

7.8.1 Describe the technique used for evidence synthesis and/or meta-analysis. Include a rationale for the studies selected, details of the methodology used and the results of the analysis.

Not appropriate

7.8.2 If evidence synthesis is not considered appropriate, give a rationale and provide a qualitative review. The review should summarise the overall results of the individual studies with reference to their critical appraisal.

The identified studies relating to ReCell are a mixture of comparative randomised controlled trials, comparative case series and non comparative case series. The comparative studies have been carried out in widely varying patient populations and evaluate ReCell – either alone or in combination with other treatments – against a variety of comparator treatments. Although there is some degree of consistency in terms of outcomes measured, the degree of heterogeneity in patient populations, interventions and study methodology precludes conventional meta-analysis. Furthermore, the lack of cross-over in characteristics between the studies means that mixed treatment comparison is also inappropriate. For these reasons we have elected to carry out a narrative review of studies carried out in burns patients in addition to a supplementary review of studies in a broader patient population relating to the management of dyspigmentation.

Randomised controlled trials in burns

Gravante 2007⁷

This is the largest published randomised controlled trial of ReCell, carried out in patients with deep partial thickness burns and was intended to investigate the use of ReCell vs early SSG – all interventions were carried out between days 3-5 post injury. Outcomes relevant to the procedure itself, healing times and long term aesthetic outcome were assessed. Patients were explicitly matched for age, gender, type and extent of burns, to ensure that any observed differences reflected the treatments used, rather than the population evaluated.

The area of burn treated was the equivalent for both groups (176 sq cm vs 180 sq cm; $p=ns$) while the mean size of donor site, was significantly smaller in ReCell treated patients (2.2 sq cm vs 110 sq cm; $p<0.001$), reflecting the fundamental difference in the treatment modalities. Mean duration of the primary operative procedure was significantly longer with ReCell (59 mins vs 20 mins; $p<0.001$).

The mean time to wound healing was comparable in the two groups (13 days vs 12 days; $p=ns$). Mean post-operative pain score was significantly lower in the ReCell group (3.3 vs 6.8; $p=0.03$). Long term aesthetic results with regard to pigmentation and vascularity were equivalent between the two groups (scores not reported). There were no interoperative or postoperative adverse events reported in either group.

Overall, this study demonstrates equivalence between ReCell and SSG with regard to wound healing and ultimate result in patients with deep partial thickness burns, although post-operative pain and donor site size were significantly better in the ReCell-treated group.

Wood 2012⁸

This is a pilot RCT that provides a useful insight into the relative value of Biobrane, ReCell + Biobrane or SSG in a paediatric scald population. The

numbers involved were small – 4 patients each for SSG and Biobrane alone and 5 for Biobrane + ReCell – so formal statistical analysis was not carried out. Despite this limitation, the study gives us a perspective on clinical outcomes that is informative.

The four patients allocated to SSG were expected to undergo the procedure on day 10 of the injury and all but one did so. Of the patients allocated to Biobrane alone, one required grafting, while none of the patients to Biobrane + ReCell. Median time to healing was the same in both the Biobrane and Biobrane/ReCell groups (16 days) – less than half that observed in the SSG group (36.5 days). Post-intervention pain scores also appeared lower (5.5, 2.0, 3.0 respectively). Long term scar outcomes were similar between groups.

The study also assessed healthcare costs. Although it is possible to identify potential areas of saving for some elements with ReCell (dressing costs, theatre costs, admission costs), the huge variation in individual patient expenditure, largely reflecting length of stay, make it difficult to draw any clear conclusions.

Overall, the study provides some reasonable data, suggesting once again that both Biobrane and Biobrane/ReCell can offer equivalent outcomes to SSG, while allowing healing to take place more quickly and allowing reduced expenditure in some care elements.

Observational studies in burns

Park 2013⁹

This large retrospective observational study evaluated 770 burns patients treated with either SSG alone (n=387), ReCell + SSG (n=264), ReCell alone (n=73) or cultured epithelial cell +/- SSG (n=46). The latter group relates to a technology that is no longer available and is therefore not considered further.

The study assessed the impact of treatment type on the risk of burn wound infection, graft loss and length of hospital stay by means of a multivariate

logistic regression analysis, comparing the impact of both ReCell-containing regimens versus SSG alone. After correction for potential confounders, there was found to be no significant difference between SSG and ReCell alone (HR = 0.78; p=0.98) or ReCell + SSG (HR 1.23; p=0.97) for the wound infection outcome. Similarly, there was no significant difference in the risk of graft loss for either ReCell (HR=0.89; p=0.09) or ReCell + SSG (HR=1.56; p=0.67). With regard to length of hospital stay, ReCell patients had a significantly lower length of stay (HR=0.70; p<0.01), while there was no significant difference with ReCell + SSG (HR=0.98; p=0.85).

It should be borne in mind that the patient groups were not matched a priori in this retrospective analysis, and it is possible that the decision to use one treatment modality over another may have been governed by factors that were not controlled for in the regression analysis. Nonetheless, this study provides good evidence that the risk of wound infection or graft loss associated with ReCell is at least as good as that seen with SSG and that, when used alone, ReCell-treated patients are able to be discharged from hospital significantly earlier than those undergoing SSG (whether with or without ReCell).

There were three other comparative case series identified in the literature search:

- **Dunne 2012** ¹⁰
- **Rawlins 2013** ¹¹
- **Rawlins 2011** ¹²

Dunne 2012 ¹⁰ reported on 40 children with scalds treated using an escalating clinical pathway (Biobrane alone => ReCell + Biobrane => SSG) according to the depth of the scald. All treatments were instituted within the first 48 hours of treatment, with the intention of achieving early healing. 71% of full thickness burns, 62% of mid and deep dermal burns and 70% of superficial dermal burns were successfully healed without further grafting using this strategy.

Although this study does not allow a direct comparison of treatments to be carried out, as the populations for each modality were different, it nonetheless demonstrates that ReCell can be successfully integrated into a standard treatment pathway in a burns unit.

Rawlins 2013 ¹¹ reported on 26 children with burns managed with either ReCell or SSG. Patients were treated according to the preference of the consultant in charge, meaning that patients with smaller burns tended to undergo SSG (mean TBSA: 2.9%) while children with larger burns were more likely to be treated with ReCell (mean TBSA: 6.5%). Burns outcome was evaluated by five independent clinicians using a VAS at four months, and showed no difference between treatments (mean score 3.9 for both groups). Mean duration of physiotherapy follow-up was shorter for ReCell treated patients (21 days vs 40 days) while duration of the initial operative procedure was longer (87 minutes vs 58 minutes).

This study, once again, is subject to the limitations of the non-randomised design, but supports the hypothesis that ReCell is at least as effective as SSG, while potentially offering savings in long term treatment support.

The third comparative series, Rawlins 2011 ¹², compares outcomes in 5 patients with deep flame burns treated with ReCell + Biobrane and 10 matched controls treated with SSG. The abstract does not detail which criteria were used for matching patients with controls. Mean TBSA was 15% (range 9-24%).

ReCell + Biobrane was associated with a considerably shorter healing time (18 days vs 48 days; p value not given) and analgesic requirements were less (numerical data not given). At six months, the quality of scar, as assessed by the Vancouver Scar Assessment, was also better in the ReCell + Biobrane group (numerical data not given).

Although there is limited data given in this abstract, the information supplied supports the use of ReCell with Biobrane in patients with larger, deep dermal burns, where SSG would ordinarily be the treatment of choice.

Below is a brief review of five further non-comparative case series that can complement our understanding of the role of ReCell in burns:

- ***Cui 2013 (unpublished)***²³
- ***Echlin 2012a***¹³
- ***Echlin 2012b***¹⁴
- ***Palombo 2012***¹⁵
- ***Sen 2012/Philp 2013***^{16,22}



Echlin 2012a¹³ presents data on 5 patients with mid to deep dermal burns affecting the whole face, who had been primarily treated with allografts 0-2 days post burn but who were found to have unhealed burns at day 9-11 in four cases and at 23 days in one case. The four patients treated at day 9-11 were all healed by day 7 post surgery (mean time to healing 5 days) while the late-presenting patient showed improvement but required a further small allograft to complete the healing.

Echlin 2012b¹⁴ describes 9 patients with 11 donor sites used to provide skin grafts. 8 of the 9 were burns patients and had a mean skin loss of 10% on the donor sites. All sites healed by day 14 (mean time to healing day 9) and in two patients, the donor sites were able to be further harvested on days 14 and 20 respectively. In two patients, there were two or more donor sites only one of which was treated with ReCell. In one patient the ReCell treated site was healed within 7 days while the untreated site took until day 29 to heal. In the second patient, the treated site was healed within 13 days, but the untreated site was not healed until day 20.

Palombo 2012¹⁵ gives brief details of 6 children with hypertrophic scars following burn injuries. After dermabrasion and ReCell, complete re-epithelialisation was achieved by day 10 in all patients. Satisfactory skin pigmentation and texture was reported in all cases by 3 months post-operatively.

Sen 2012¹⁶ and Philp 2013²² present data from the same sequence of patients with extensive burns, who underwent dermal skin grafting. In these 10 patients there was a shortage of viable donor skin to achieve coverage of burn injuries. After all available sites had been harvested for standard SSGs, a second dermal skin graft was obtained from the base of the donor site. After application to the wound, ReCell was used to colonise both dermal graft and the donor site with epithelial cells.

Two of the 10 patients died as a result of their burns. Amongst the 8 survivors, Average time to healing was 12 days for the burn sites and 14 days for the donor sites. Ultimate scar appearance was assessed as being no worse than would have been expected for a conventional SSG and donor site.

These case series, while lacking the robustness of a randomised controlled trial, give a clear impression of the benefits that can be achieved with ReCell in a broader range of clinical situations than is defined in the scope: long term scar management, donor site healing and making dermal skin grafting a possibility. The Echlin 2012b abstract¹⁴ is particularly compelling with regard to donor site healing, especially as it includes two within-patient comparisons of healing times for ReCell-treated donor sites with untreated sites.

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This aspect of ultimate scar aesthetics is a particularly important outcome for patients, especially those with darker skins, where depigmented scars are particularly obvious. In order to understand this aspect of ReCell's benefit further, we undertook a supplementary literature search for studies investigating this outcome. While much of the data

identified relates to patients with conditions other than burns, the technology and means of application is identical to that used with burns injuries and we believe it is therefore reasonable to use this data to inform our understanding of ReCell.

Studies in dyspigmentation

Cui 2013 (draft manuscript)²³

The findings of this paper have already been discussed in the burns section of the narrative review above.

Cervelli 2009a¹⁸

This paper presents the results of 30 adult patients with post-traumatic scars with unacceptable aesthetic appearance that had proved resistant to previous treatment with intralesional steroids, chemical peeling, laser therapy, microdermabrasion or dermabrasion. 11 patients had hypopigmentation, 2 had hyperpigmentation, 3 had hypertrophy or keloid formation and 14 had skin contracture. Surgery was performed 15-16 months post injury. After dermabrasion, ReCell was used to re-epithelialise the affected area.

All patients completed at least one year's follow-up and were assessed for cosmetic result. Histological examination identified pigmented melanocytes as being present in 18 patients (60%) at 5 weeks post operatively and in 28 patients (93%) by 7 weeks. Subjective assessment of scar pigmentation was carried out at 1 year, using a modified version of the Vancouver Scar Scale, with scars being assessed as being normal or slightly, moderately or severely abnormal. 18 patients (60%) rated their pigmentation as being normal, with the remainder rating the pigmentation as being slightly (n=9; 30%) or moderately (n=3; 10%) abnormal. No patient rated their pigmentation as being severely abnormal.

Surgeons rated the overall functional and cosmetic result as good or excellent in 24 cases (80%) while patients scored a similar rating in 26 cases (87%).

Cervelli 2009b¹⁹

This study presents the effect of ReCell on skin pigmentation in 15 adult patients with stable vitiligo, carried out over a 2 year period. Three weeks after ReCell was used, 6 patients (40%) had visible repigmentation, rising to 9 patients (60%) by five weeks. When assessed at six months, 80% of patients had greater than 75% repigmentation in the treated area, with the remaining 20% having 25-50% repigmentation. 10 patients (67%) rated the result as excellent, while 5 (33%) patients rated it as good. No patients rated their result as fair or poor.

Mulekar 2008²⁰

This pilot study compared two modalities of autologous cell treatment in 5 patients with stable vitiligo. Each patient had two lesions in the same anatomical location treated, one with ReCell and another with melanocyte-keratinocyte transplantation (MKT). The latter procedure involves a similar process of separation of the epidermal cells from a thin shave skin biopsy, although in this case the sample requires overnight processing in a laboratory.

4 months after the procedure, the pigmentation results were assessed. In two cases, 100% repigmentation was achieved using both techniques; in one case neither intervention was able to achieve any repigmentation. Of the two remaining patients, in one case ReCell was more successful (40% vs 30%) while in the second, MKT was more effective (65% vs 100%). The author concluded that the repigmentation was similar with the 2 methods.

Daniel 2013²¹

This is an abstract describing an interim report of a randomised controlled trial comparing ReCell and SSG (minigrafting) in the management of vitiligo. 14 patients with paired lesions were treated with both technologies and the degree of repigmentation assessed at 12 months. Limited data are available, but the authors report 15% of patients with full repigmentation with ReCell at 12 months, compared to 12% with minigrafting.

Although these studies have been carried out across a range of different pathologies, the consistent finding from 4 of the five studies is that treatment with ReCell can deliver good or excellent repigmentation in around 60-80% of patients treated, even where multiple previous treatments have failed. In the fifth study (Daniel 2013 ²¹) data on this outcome were not provided in this form in the abstract.

The disruption of normal melanocyte presence and function within wounded skin results in dyspigmentation, highlighting the presence of otherwise less noticeable scars, and in the case of hypopigmentation, leaving the skin without normal protection from ultraviolet radiation and the associated risk of skin malignancy ^{24, 25}. It is well documented that the undesirable aesthetics of scars can lead to profound psychological implications ^{26,27}.

Although it is difficult to directly extrapolate these results to patients suffering acute burns, similar levels of effectiveness may well be achievable and the evidence provides support for the successful transplantation of pigment producing cells (functioning melanocytes) with ReCell.

7.9 *Interpretation of clinical evidence*

- 7.9.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology.

There is good evidence from both prospective and retrospective studies that the use of ReCell is at least as effective as SSG in achieving wound healing in the acute management of partial thickness burns in both adults and children and achieves comparable cosmetic and functional scar results.

This benefit is not associated with any known device-related adverse events and patients who undergo treatment with ReCell have no greater risk of wound infection or graft loss than patients treated with SSG.

The addition of ReCell to SSGs and dermal grafts allows more rapid epithelialisation of the burn site than would have been achieved with SSG alone.

The use of ReCell with biological dressings such as Biobrane is well established. This combination offers comparable benefits to SSG but is associated with more rapid healing, lower costs and shorter length of hospital stay. There is insufficient evidence to quantify any incremental benefit of this combination over either component used alone.

ReCell can be used to treat donor sites for SSGs and allows more rapid healing. In patients with large burns, this approach is advantageous, as it allows skin to be re-harvested from the site more quickly than would otherwise be the case.

When used to reprofile or repigment established burns scars, ReCell yields high rates of improvement in the final aesthetic result. This beneficial result on pigmentation is backed up by similarly positive results in patients with vitiligo treated with ReCell.

- 7.9.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

There is one large randomised controlled trial ⁷ and one large retrospective regression analysis ⁹ of ReCell that underlie its safety and efficacy in the acute management of burns. The remaining evidence derives from two small randomised controlled trials^{8,21} and a number of case series – both comparative and non-comparative. Inevitably, the lack of multiple randomised controlled trials means that making robust comparisons of different treatment modalities is challenging. Clearly the design of a retrospective case series does not include the advantages of randomisation and few of the measures described can be appropriately analysed from a statistical standpoint.

This limitation is compounded by the inherent heterogeneity of burns patients. Differences in age, depth, location and extent of burns mean that burns management is not readily amenable to standardised management protocols – a fact reflected by the lack of clinical guidelines highlighted in section A.

These combine to mean that the results presented are probably best understood in qualitative rather than quantitative terms. For instance, we can say with some confidence that ReCell is at least as effective as SSG in partial thickness burns and that length of hospital stay is likely to be less. Converting this comparison into an estimate of the number of days involved, however, would extend beyond the limits of the study designs and would, in any case be highly dependent on the patient populations being treated.

On the positive side, the wide range of patient types and treatment strategies evaluated in the case series, and the absence of adverse events, gives us a degree of confidence that the results seen are likely to be applicable and safe across a broad range of patients.

7.9.3 Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and system-benefits described in the scope.

The scope requires that evidence should address a) patients with partial thickness burns and scalds not requiring SSG and b) patients with large area burns, whether full thickness or deep partial thickness, where SSG may be required. Both these patient groups have been adequately addressed by the evidence presented, with acute management of the burn, donor site management and late scar revision being covered. Although not a study, additional cases of ReCell combined with SSG may be seen illustrated in O'Neill 2012 ²⁸.

Secondly, the scope asks that the interventions considered should be either a) ReCell alone or in combination with biosynthetic or standard dressings or b) skin mesh graft in combination with ReCell. Once again, both these interventions have been covered within the presented evidence, either alone or in comparison with each other

Thirdly, we are asked to consider comparisons with either biosynthetic or standard dressings alone for partial thickness burns or SSG with or without biosynthetic dressing in large area burns. These comparators have all been covered by the presented evidence, although all possible permutations have not been addressed – for instance there is insufficient evidence to state how ReCell combined with biosynthetic dressings compares with ReCell combined with standard dressings.

Fourthly, there is a range of twelve outcomes that we are asked to consider. Most of these have been covered for some of the scenarios investigated although not all are covered for all combinations. Thus, for instance, we have good data on wound infection rates for ReCell alone, ReCell + SSG and SSG alone in a range of different burn types, but data on surgical procedures and theatre time is not available for all of these three options. No data are available for some outcomes (growth rate in children, and transfusion rates). Partial data exists for others: for instance we can describe the impact of the

different treatment options on length of hospital stay, but this cannot be expressed as length of stay per % TBSA.

Finally, we are asked to consider special issues relating to the porcine origin of trypsin in ReCell and the impact of ReCell on skin pigmentation. We have presented extensive data on skin pigmentation, derived from both burns and non-burns patients. Regarding the porcine origin, we are not able to offer any information on the acceptability of the technology to individuals with religious prohibitions relating to pigs.

7.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

The critical issue regarding external validity relates not to the technology and the study results presented but to the inherent heterogeneity of burns patients. As already discussed, management strategies for burns are essentially individualised and it is very difficult to define standard patterns of care. Whilst general principles as to the areas where ReCell may be most advantageously used can be inferred from the evidence, it will never be possible, regardless of the future extent of the evidence, to draw firm lines and define protocols.

Data from Wakefield (Dunne 2012¹⁰) have shown how ReCell can be effectively implemented into a general care pathway, but the actual treatment used will always depend on the individual medical, social and cultural characteristics of the individual patient.

7.9.5 Based on external validity factors identified in 7.9.4 describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

ReCell as an adjunct to the existing care pathway is suitable for all burn surgeries, ranging from donor site treatment¹⁴ to burn injury treatment alone and in combination with conventional skin grafting. It has been shown to be particularly well suited for mixed (including indeterminate) depth burns¹⁰, darker skin patients²³, facial burns¹³, paediatric scalds^{8,10} and those with extensive burns^{16, 22}.

Section C – Economic evidence

Section C requires sponsors to present economic evidence for their technology.

All statements should be evidence-based and directly relevant to the decision problem.

The approach to the de novo cost analysis expected to be appropriate for most technologies is cost-consequence analysis. Sponsors should read section 7 of the Medical Technologies Evaluation Programme Methods guide on cost-consequences analysis, available from www.nice.org.uk/mt

Sponsors are requested to submit section C with the full submission. For details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

8 Existing economic evaluations

8.1 Identification of studies

The review of the economic evidence should be systematic and transparent and a suitable instrument for reporting such as the PRISMA statement ([REDACTED]).

A PDF copy of all included studies should be provided by the sponsor.

- 8.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in section 10, appendix 3.

The search strategy set out to identify studies in one of three qualifying groups:

1. Economic evaluations of ReCell in the acute treatment of burns
2. Economic evaluations of biological or other dressing types in the acute treatment of burns
3. Cost impact studies in acute burn management, regardless of intervention used

Electronic databases searched were: MEDLINE (including In Process), EMBASE and NHS Economic Evaluations Database. A broad search strategy was used to maximise the number of potential studies, as prior experience had led us to expect a relatively small number of studies would be identified. Details of the search terms used are given in Appendix 3.

After preliminary screening of abstracts for likely inclusion, full text versions of the studies were obtained. In addition to formal inclusion/exclusion assessment of these studies, reference lists were manually searched in order to identify possible further qualifying studies.

As the availability of full data is a necessary requirement for use of economic studies, no hand search of abstracts presented at medical meetings was carried out.

Finally the manufacturer was consulted in order to identify any further potentially qualifying unpublished studies.

Search dates: As cost data are time-sensitive, a decision was made to limit the search to the past 10 years (Jan 2003 – July 2013)

Perspective: We ideally wished to identify studies evaluating UK NHS expenditure. However, the expected paucity of published data meant that no strict geographical limitation was placed on the search, although any UK studies identified will be given greater weight in any subsequent use within this submission.

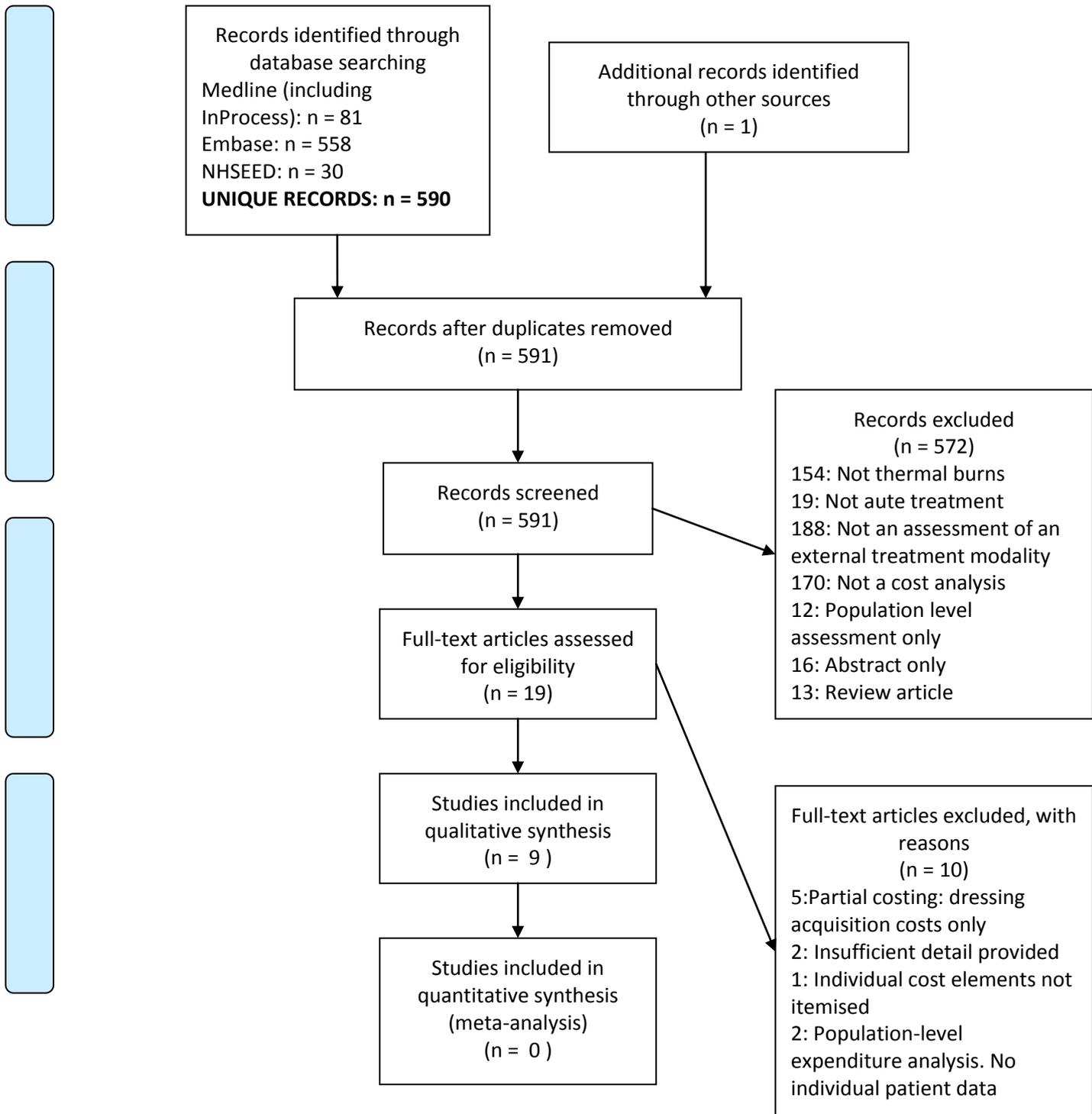
8.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table C1 Selection criteria used for health economic studies

Inclusion criteria	
Population	Adults and children undergoing treatment for flame burns and scalds of at least partial thickness
Interventions	Any specified external wound management strategy including, but not limited to ReCell and biosynthetic dressings
Outcomes	Cost of care (expenditure and/or reimbursement), cost benefit, cost utility, budget impact
Study design	Cost effectiveness analyses, cost of care analyses, budget impact analyses, other economic assessments.
Language restrictions	None
Search dates	January 2003 – July 2013
Exclusion criteria	
Population	Patients undergoing care for any injury other than flame burns and scalds
Interventions	Surgical strategies, oral or parenteral therapies, any treatment not given at the time of acute burn management
Outcomes	Non cost-based outcomes, population-level assessments (ie not based on individual patient care costs), partial cost assessment (ie insufficient to compare overall costs of care for the element assessed)
Study design	Epidemiological assessments, non-quantitative review articles
Language restrictions	None
Search dates	Published before January 2003

8.1.3 Report the numbers of published studies included and excluded at each stage in an appropriate format.

Figure 5 – PRISMA flow chart for economic literature search



8.1.4 Description of identified studies

Provide a brief review of each study, stating the methods, results and relevance to the scope. A suggested format is provided in table C2.

The search identified three qualifying cost effectiveness analyses, all evaluating two types of dressing [Carayanni 2011²⁹, Caruso 2006³⁰, Silverstein 2011³¹. There were no formal economic evaluations of ReCell or biological dressings.

All remaining studies were cost of care analyses, which were used to inform the costings and transition probabilities for the de novo model

Table C2 Summary list of all evaluations involving costs

Study name (year)	Location of study	Summary of model and comparators	Patient population (key characteristics, average age)	Costs (intervention and comparator)	Patient outcomes (clinical outcomes, utilities, life expectancy, time to recurrence for intervention and comparator)	Results (annual cost savings, annual savings per patient, incremental cost per QALY)
Carayanni 2011 ²⁹	Burn centre in Athens, Greece	Cost effectiveness analysis of oil-based vs povidone iodine based dressings	211 patients undergoing acute treatment of burns not requiring surgery Mean age was 42.6 in oil group and 42.7 in iodine group 109 had superficial	Hospital stay cost Staff time costs Dressing costs Laboratory costs Medication costs	Two main indicators of effectiveness: 1. For deep partial burns effectiveness defined by a reduced length of stay in one group compared to the other 2. For superficial burns (outside scope) the time to achieve a 50%	Mean total cost of care per patient was lower in the oil-based group: €529.66 vs €566.21 (all) €579.83 vs €582.15 (deep) Oil based dressings were associated with a

			partial thickness burns (Outside scope) 102 had deep partial thickness burns. Mean TBSA was 9.89% and 10.26% in the two groups	All measured in 2006 Euros	reduction in transepidermal water loss defined effectiveness Data on pain, qualitative wound evaluation and complication rates were also collected	mean reduction in length of stay of one day Oil based dressings consequently dominated povidone iodine based dressings
Comment: This study evaluated a group of patients who were explicitly not expected to require surgery. This implicitly excludes those with indeterminate burns depth and therefore only covers the milder end of the scope-defined patient group						
Caruso 2006 ³⁰	8 Burn Centres in USA	RCT of two types of dressing (Aquacel or silver sulfadiazine [SS]) with cost effectiveness analysis	82 patients with burns of varying depths, excluding those likely to require grafting. Mean age 29.4 in Aquacel group and 24.0 in SS group Mean TBSA was 12.0% and 10.8% in the two groups	Costs of care included: Dressing acquisition costs Staff time costs Medication costs Hospital stay costs were not included All costs in 2004 US\$	The primary endpoint was the cost effectiveness of Aquacel vs SS, based on a primary effectiveness endpoint defined as a comparison of the proportion of patients achieving full re-epithelialisation within 21 days Data were also collected for redressing pain, comfort and safety	Mean total cost of care was \$1040.00 for Aquacel vs 1180.80 for SS Re-epithelialisation was achieved at 21 days in 73.8% of Aquacel patients vs 60.0% of SS patients Aquacel therefore dominated SS
Comment: This study, like the previous one, excluded patients with indeterminate wound depth and therefore only applies to a subset of the scope population. Additionally, hospital stay costs were not incorporated in the analysis						
Silverstein	10 burns	RCT	100 patients aged	Acquisition	Proportion with 100% re-	78.3% of Silicone

2011 ³¹	centres in the USA	comparing two types of dressing: Silver-containing soft silicone foam dressing (Silicone) and Silver sulfadiazine cream (SS). Cost data were collected as a secondary outcome in a subset of 40 patients (100 total). Data used to estimate cost effectiveness (cost per healed burn)	5+ with a second degree (partial thickness) burn area of 2.5% - 20%. Mean age 37.0 (Silicone) and 39.2 (SS) Mean TBSA treated 5.64% (Silicone) and 4.93% (SS)	cost of dressings Cost of staff time to change dressings Analgesia cost All costs in 2009 US\$	epithelialisation at 20 days post burn Dressing and analgesic costs Primary outcome was defined as incremental cost effectiveness, based on the two outcomes above, although cost data were only gathered from 40% of patients Data also collected on % healed at 1 and 2 weeks post burn, mean length of stay, pain, ease of use, microbiological colonisation and safety	patients healed by 21 days vs 66.2% of SS patients. Mean total cost was \$309 in Silicone group and \$514 in SS group Silicone therefore dominated SS
Comment: This study only collected direct costs associated with the dressings tested and does not therefore yield an overall cost of care figure						
Fong 2005 ³²	Burn Centre in Perth, Australia	Audit reporting clinical results obtained with two different dressing types: Acticoat	Four pairs of burns patients matched for TBSA and burn depth.	The following costings were documented for the 8 patients: Hospital stay	The primary endpoint for this costing sub-audit was the total cost of care for the four patients on each dressing type excluding antibiotic, surgery, cultured epithelial autograft	Average total cost of care per patient was \$19,726 in the Acticoat group and \$27,339 in the Silvazine group. Dressing acquisition

		and Silvazine. Within the data is a detailed cost comparison for four matched pairs of patients receiving treatment with one or the other dressing type		costs Dressing costs All costs in 2002 US\$ Note: although table 5 in this paper quotes Aus\$, in all other sections, the results are said to be US\$	and staff costs.	costs accounted for \$946 and \$1533 per patient respectively , the remainder being due to hospital costs.
Comment: Although this study is limited by the exclusion of certain cot elements, the level of detail provided make this a useful contribution to the understanding of true costs of care in burns						
Pellatt 2010 ³³	Paediatric burns centre in Bristol, UK	Assessment of cost of care for major paediatric burns	3 patients with major burns (30-40% TBSA) – mixed partial and full thickness Patients aged 3, 4, and 12 years	Fully detailed costing including: Staff time Theatre time Consumables Ward costs Invasive procedures Medications Laboratory Imaging + 20% uplift for overheads	Main outcome was descriptive analysis of the costs in each case	Total costs ranged from £55,355 to £74,494 (mean £63,157) Largest clinical components were ward costs (ICU/HDU + standard ward) and theatre time. Dressing costs accounted for 5% of total costs

				All costs in 2009 £		
Comment: Although this study is very small and included only severely burned children, this paper is a valuable source of information on NHS unit costs to validate the assumptions used in our de novo model						
Hemington-Gorse 2008 ³⁴	Welsh Burns Centre, Swansea	Assessment of cost of care for major burns: comparison between actual expenditure and HRG costing	Records from 409 patients admitted over 2005/6 were used to generate unit costings for all elements of care. These values were applied to three patients to produce individual costings. Patient ages were 35, 31, and 45. TBSA were 27-48%	Detailed costing (as for Pellatt above). Staff costs, drugs, consumables and indirect costs were assessed for each area to generate a cost per unit time for: ITU Theatre Dressing room Low dependency ward. Individual high cost items were separately accounted for. All expressed as 2005/6	Narrative description of cost of for each of the three patients. Parallel assessment of payment accrued using HRG tariff	Cost of care ranged from €121,496 - €761,205. Theatre time and ITU stay were the most expensive components. HRG-based costings were 39%, 49% and 6% less than this for the three patients assessed

				Euros		
Comment: Once again, a small study with severely burned patient but, like Pellat 2010, it provides UK unit costs for use in our model						
Griffiths 2005 ³⁵	Regional burns unit, Bristol, UK	Assessment of cost of care for 3 paediatric scalds	Three patients aged 13 months, 21 months and 2 years with scalds affecting 4%, 2% and 3% TBSA. All partial thickness burns	Comprehensive cost assessment including staff costs for the following elements: Ward costs Theatre visits Dressings Medications All costs expressed as 2004 £.	Narrative description of costs incurred in the management of the three patients. Comparison made with the equivalent HRG-based tariff	Total costs were £2169, £2063 and £1317 Equivalent HRG costings were 50%, 48% and 35% less than this
Comment: This study provides similar information to the previous two analyses, but this time focussing on more minor burn injuries						
Ahn 2012 ³⁶	Burn centre in Sydney, Australia	Detailed cost of care analysis of 20 adult patients	Random sample of 20 adult patients (mean age 40.5) admitted to burns unit, stratified into four categories by extent of burns: 0-9% TBSA 10-19% TBSA 20-29% TBSA 30% + TBSA.	Comprehensive assessment including the following elements: Ward stay Staff costs Theatre visits Dressings Medications	Costing data were used to estimate: Cost per % TBSA Cost per hospital day Regression analysis to develop equation for estimation of total costs based on TBSA	Total cost of care was \$2.45million (\$122,456 per patient). By group: Gp 1: \$3,884 per pt Gp 2: \$16,536 per pt Gp 3: \$28,312 per pt Gp 4: \$49,233 per pt Overall cost per % TBSA was \$6,264

			Overall mean TBSA was 19.6%. In the four groups it was 3.1%, 13.2%, 22.6% and 39.3% respectively	Lab tests Imaging Fluid and nutritional support All costs in 2008 AUS \$		As costs per TBSA was not a linear function, a regression formula to estimate the cost more accurately was presented
Comment: the methodology here is similar to that used in Rawlins (unpublished) which is described below and was used to generate costings for our own model. It therefore helps to validate the model.						
Rawlins 2013 ³⁷ Unpublished data – content provided as spreadsheet	Burns centre in Wakefield, UK				Primary objective was to describe costs associated with each patient.	
Comment: This work is not yet completed, but it provides a good insight into the costs of current UK practice across a wide range of burns severity and is therefore included here.						

8.1.5 Provide a complete quality assessment for each health economic study identified. A suggested format is shown in table C3.

Table C3 Quality assessment of health economic studies

Study name Carayanni 2011 ²⁹		
Study design		
Study question	Response (yes/no/not clear/N/A)	Comments
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	No	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Generated within this study
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	As above
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	n/a	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	n/a	

13. Were the details of the subjects from whom valuations were obtained given?	n/a	
14. Were productivity changes (if included) reported separately?	n/A	
15. Was the relevance of productivity changes to the study question discussed?	Yes	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	No	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	Stated as 2006 Euros
20. Were details of any model used given?	n/a	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	n/a	
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	No discount in base case because time horizon <1year. Sensitivity analysis explored discounting on basis of economic contraction
24. Was the choice of rate justified?	n/a	
25. Was an explanation given if cost or benefits were not discounted?	Yes	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	Only discount rate was explored
29. Were the ranges over which the parameters were	Yes	

varied stated?		
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	n/a	
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name Caruso 2006³⁰		
Study design		
Study question	Response (yes/no/not clear/N/A)	Comments
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	No	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	No	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	

7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Generated within this study
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	As above
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	n/a	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	n/a	
13. Were the details of the subjects from whom valuations were obtained given?	n/a	
14. Were productivity changes (if included) reported separately?	n/a	
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	Stated as 2004 US dollars
20. Were details of any model used given?	n/a	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	n/a	

22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	No	21 day study, so discounting not justified
24. Was the choice of rate justified?	n/a	
25. Was an explanation given if cost or benefits were not discounted?	n/a	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	No	No sensitivity analysis
28. Was the choice of variables for sensitivity analysis justified?	n/a	
29. Were the ranges over which the parameters were varied stated?	n/a	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	n/a	
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name Silverstein 2011³¹		
Study design		
Study question	Response (yes/no/not clear/N/A)	Comments
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Generated within this study
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	n/a	Yes (see above)
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	n/a	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	n/a	
13. Were the details of the subjects from whom valuations were obtained given?	n/a	
14. Were productivity changes (if included) reported separately?	n/a	

15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	<u>US\$ 2009</u>
20. Were details of any model used given?	n/a	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	n/a	
22. Was the time horizon of cost and benefits stated?	n/a	
23. Was the discount rate stated?	n/a	
24. Was the choice of rate justified?	n/a	
25. Was an explanation given if cost or benefits were not discounted?	n/a	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	No	No sensitivity analysis
28. Was the choice of variables for sensitivity analysis justified?	n/a	
29. Were the ranges over which the parameters were varied stated?	n/a	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	n/a	
31. Was an incremental analysis reported?	No	
32. Were major outcomes	Yes	

presented in a disaggregated as well as aggregated form?		
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name Fong 2004³²		
Study design		
Study question	Response (yes/no/not clear/N/A)	Comments
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	No	Cost outcomes were secondary to the clinical objectives of the study
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	No	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	Cost of care analysis only
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
8. Was/were the source(s) of effectiveness estimates used stated?	n/a	No CER generated
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	n/a	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	n/a	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	No	
12. Were the methods used to value health states and other benefits stated?	n/a	
13. Were the details of the subjects from whom valuations were obtained given?	n/a	
14. Were productivity changes (if included) reported	n/a	

separately?		
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	No	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	Stated as 2002 AUS\$
20. Were details of any model used given?	n/a	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	n/a	
22. Was the time horizon of cost and benefits stated?	n/a	
23. Was the discount rate stated?	n/a	
24. Was the choice of rate justified?	n/a	
25. Was an explanation given if cost or benefits were not discounted?	n/a	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	No	No sensitivity analysis
28. Was the choice of variables for sensitivity analysis justified?	n/a	
29. Were the ranges over which the parameters were varied stated?	n/a	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	n/a	
31. Was an incremental analysis reported?	No	

32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name Pellat 2010³³		
Study design		
Study question	Response (yes/no/not clear/N/A)	Comments
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	n/a	Descriptive cost of care analysis
5. Were the alternatives being compared clearly described?	n/a	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
8. Was/were the source(s) of effectiveness estimates used stated?	n/a	No CER generated
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	n/a	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	n/a	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	n/a	
13. Were the details of the subjects from whom valuations were obtained given?	n/a	
14. Were productivity changes (if included) reported	n/a	

separately?		
15. Was the relevance of productivity changes to the study question discussed?	No	Paediatric population
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	UK £. Assumed date 2009
20. Were details of any model used given?	n/a	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	n/a	
22. Was the time horizon of cost and benefits stated?	n/a	
23. Was the discount rate stated?	n/a	
24. Was the choice of rate justified?	n/a	
25. Was an explanation given if cost or benefits were not discounted?	n/a	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	No	No sensitivity analysis
28. Was the choice of variables for sensitivity analysis justified?	n/a	
29. Were the ranges over which the parameters were varied stated?	n/a	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	n/a	
31. Was an incremental analysis reported?	No	

32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name Hemington-Gorse 2008³⁴		
Study design		
Study question	Response (yes/no/not clear/N/A)	Comments
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	n/a	Descriptive cost of care analysis
5. Were the alternatives being compared clearly described?	n/a	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
8. Was/were the source(s) of effectiveness estimates used stated?	n/a	No CER generated
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	n/a	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	n/a	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	n/a	
13. Were the details of the subjects from whom valuations were obtained given?	n/a	
14. Were productivity changes (if included) reported	n/a	

separately?		
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	Euros. Assumed date 2006
20. Were details of any model used given?	n/a	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	n/a	
22. Was the time horizon of cost and benefits stated?	n/a	
23. Was the discount rate stated?	n/a	
24. Was the choice of rate justified?	n/a	
25. Was an explanation given if cost or benefits were not discounted?	n/a	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	No	No sensitivity analysis
28. Was the choice of variables for sensitivity analysis justified?	n/a	
29. Were the ranges over which the parameters were varied stated?	n/a	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	n/a	
31. Was an incremental analysis reported?	No	

32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name Griffiths 2005³⁵		
Study design		
Study question	Response (yes/no/not clear/N/A)	Comments
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	n/a	Descriptive cost of care analysis
5. Were the alternatives being compared clearly described?	n/a	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
8. Was/were the source(s) of effectiveness estimates used stated?	n/a	No CER generated
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	n/a	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	n/a	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	n/a	
13. Were the details of the subjects from whom valuations were obtained given?	n/a	
14. Were productivity changes (if included) reported	n/a	

separately?		
15. Was the relevance of productivity changes to the study question discussed?	No	Paediatric population
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	UK £. Assumed date 2004
20. Were details of any model used given?	n/a	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	n/a	
22. Was the time horizon of cost and benefits stated?	n/a	
23. Was the discount rate stated?	n/a	
24. Was the choice of rate justified?	n/a	
25. Was an explanation given if cost or benefits were not discounted?	n/a	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	No	No sensitivity analysis
28. Was the choice of variables for sensitivity analysis justified?	n/a	
29. Were the ranges over which the parameters were varied stated?	n/a	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	n/a	
31. Was an incremental analysis reported?	No	

32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name Ahn 2012 ³⁶		
Study design		
Study question	Response (yes/no/not clear/N/A)	Comments
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	n/a	Descriptive cost of care analysis
5. Were the alternatives being compared clearly described?	n/a	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
8. Was/were the source(s) of effectiveness estimates used stated?	n/a	No CER generated
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	n/a	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	n/a	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	n/a	
13. Were the details of the subjects from whom valuations were obtained given?	n/a	
14. Were productivity changes (if included) reported	n/a	

separately?		
15. Was the relevance of productivity changes to the study question discussed?	No	Mentioned in passing in the introduction
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	Yes	Results presented as 2008 Aus\$. Main results also given in US \$
20. Were details of any model used given?	n/a	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	n/a	
22. Was the time horizon of cost and benefits stated?	n/a	
23. Was the discount rate stated?	n/a	
24. Was the choice of rate justified?	n/a	
25. Was an explanation given if cost or benefits were not discounted?	n/a	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	No	No sensitivity analysis
28. Was the choice of variables for sensitivity analysis justified?	n/a	
29. Were the ranges over which the parameters were varied stated?	n/a	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	n/a	
31. Was an incremental analysis reported?	No	

32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

No table has been provided for Rawlins 2013³⁷ as this is uncompleted work, without a full draft of the paper available for assessment.

9 De novo cost analysis

Section 9 requires the sponsor to provide information on the de novo cost analysis.

The de novo cost analysis developed should be relevant to the scope.

All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.

Note that NICE cites the price of the product used in the model in the Medical Technology guidance.

9.1 *Description of the de novo cost analysis*

9.1.1 Provide the rationale for undertaking further cost analysis in relation to the scope.

There have been no published economic analyses that allow us to answer the two questions posed in the scope, therefore de novo analyses are required.

Patients

9.1.2 What patient group(s) is (are) included in the cost analysis?

Patients of any age presenting for acute care of partial thickness burns or scalds, where there is no immediate need for mesh grafting. The second patient group (patients requiring meshed graft) has not been modelled – for the rationale please see

Technology and comparator

9.1.3 Provide a justification if the comparator used in the cost analysis is different from the scope.

For the first decision problem, the comparators used in the analysis are as defined in the scope: ReCell +/- biosynthetic dressing (Biobrane) vs conventional dressings or Biobrane alone

For the second decision question defined in the scope, we have not presented a model, as there is insufficient evidence to feed the input parameters.

The main indication for the use of ReCell with a meshed SSG is in patients with extensive burns, in whom a shortage of available unburned skin means that complete epithelial coverage cannot be achieved in a single step. With a traditional or small-mesh graft, part of the burn must be covered first, while waiting for the donor sites to heal sufficiently to allow re-harvesting. With ReCell, a larger mesh graft can be used, with the interstices being seeded with epithelial cell. This reduces the total time required to achieve 100% epithelial coverage (feedback from clinical advisors).

If ReCell is also used to seed the donor sites, the time elapsed before re-harvesting can be carried out is reduced, thereby also reducing the total time to healing (Echlin 2012a¹³). Given that the major drivers of costs in severely burned patients are the length of stay and use of theatre time (Pellat 2010³³), it seems likely that this strategy will need net savings well in excess of the cost of ReCell.

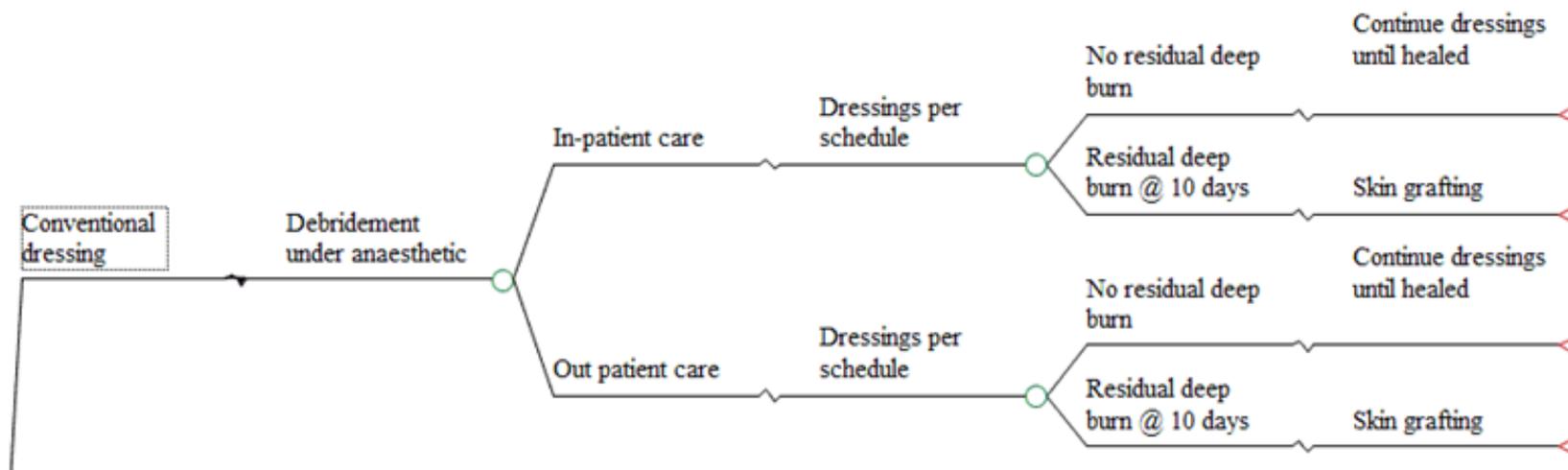
An alternative strategy in this situation is the use of cultured epidermal cells. A biopsy is harvested from the patient's own intact skin and then cultured into sheets of cells in a laboratory. These can then be used to cover the area. This process, however is costly (approximately £2,500) and time consuming – typically 2-3 weeks from the time of harvesting, thereby incurring substantial additional hospital stay costs.

Unfortunately, however, the quantitative data to support these scenarios is lacking and any model devised would be purely speculative.

In the light of our professional advice and the lack of any quantitative sources to fuel our model assumptions, we have therefore been forced to omit a cost analysis for this second decision problem.

Figure 6: Model structure

Provide a diagram of the model structure you have chosen.



9.1.4 Justify the chosen structure in line with the clinical pathway of care identified in response to question 3.3.

As discussed in the clinical section, the challenge that presents itself in the modelling of burn care management is that the pathway of care is highly individualised, depending on the precise nature, extent and depth of burn, and the characteristics of the patient being treated. The pathway outlined in section 3.3 therefore represents only broad principles of care, an approximation that is carried over into the model.

There are several distinct stages to consider where the use of ReCell may have a financial impact over one or both of the comparators over and above its acquisition cost:

1. *The requirement to remain in hospital for treatment.* Conventional dressings require regular renewal – this may be carried out daily or on alternate days, depending on the policy in the individual unit (step 2, section 3.3). This process, by exposing the burn, is a potential source of infection and must therefore be carried out in a sterile environment (theatre or sterile dressing room). It is also potentially painful and therefore, especially in children, strong analgesia or general anaesthesia may be required. For ReCell or Biobrane the wound surface is left covered until formal reassessment at day 10-12 (Step 3, section 3.3). Until this point, generally only the secondary superficial dressing requires changing, a process that does not require the use of specialist sterile facility and may be carried out in out-patients, if required. This means that conventionally treated patients are more likely to remain in hospital than those using ReCell and/or Biobrane. This element of the process is captured in the first chance node of the model
2. *Requirement for meshed SSG.* If a wound has an area of full thickness burn, it cannot re-epithelialise from the base but depends instead on migration of cells from the wound edge. Whilst this may be sufficient for

very small areas, in practice an area of any size will require grafting with healthy epithelial tissue from elsewhere on the body. At the initial assessment (step 1, section 3.3) such areas may not be immediately obvious, with the deeply burned area only becoming apparent when it fails to heal over the course of step 2. ReCell, by populating the wound base with both keratinocytes and fibroblasts effectively functions as an early skin graft and reduces the number of patients progressing to SSG at a later stage. Neither conventional dressings nor Biobrane alone can achieve this.

This element of difference is captured at the second chance node of the model.

3. *The time to achieve re-epithelialisation.* Even if SSG is not required, the time required to heal the wound is a major cost driver for burns patients. Especially for in-patients, the daily costs incurred are substantial. ReCell, by populating the wound site with epithelial cells from the outset of treatment, is associated with faster rates of healing than conventional dressings, which rely purely on re-epithelialisation from the wound base. One advisor suggested that, in her experience, this difference results in a 25-50% reduction in healing times with ReCell, an experience matched in the RCT of Wood et al⁸, where a reduction of 56% was seen with ReCell + Biobrane. Biobrane alone, by allowing the wound to remain covered and undisturbed, also achieves a reduction in healing times. In the Wood study⁸ this effect was not quite as great as that of ReCell and Biobrane combined, although the small numbers of patients involved mean that it is impossible to know if this difference is real.

This element of the care pathway is captured in the calculation of the payoffs at the end of the non-grafted arms of the model.

An additional point of difference between ReCell and the comparators is the long term aesthetic appearance of the burn scar. Whilst it is reasonable to assume that this benefit is likely to yield cost savings in terms of a reduced

requirement for scar revision surgery, a lack of available data to populate the model means that we have restricted our analysis to the acute phase of treatment.

A Markov structure using a daily cycle would have had the potential to capture the day-to-day changes in management (and therefore cost), as in reality, the decisions to discharge or to proceed to skin grafting are not necessarily taken at a fixed time point. However, we have been unable to source sufficiently detailed data to yield daily state transition probabilities and, given the relatively small number of possible care pathways, elected to use the simple decision tree option.

9.1.5 Provide a list of all assumptions in the cost model and a justification for each assumption.

For the base case the following assumptions have been made:

1. At the time of initial treatment the burn is considered to be partial thickness with no definite areas of deep involvement. This is in keeping with the scope
2. The area of burn requiring treatment is 640 sq cm. This represents around 5-10%TBSA depending on the age/size of the patient. There are a number of reasons why this size has been chosen:
 - a. This size of burn is sufficiently severe to warrant active intervention in a burn centre where ReCell might be considered an option
 - b. Data from cost analyses carried out in both the Australia (30) UK (31) show that costs of care decline rapidly at TBSA <5%
 - c. In patients with larger burns – 20%+ TBSA – the costs of intensive care, circulatory support, multiple surgical interventions

and very extended lengths of stay are likely to override any cost differences attributable to ReCell or its comparators.

3. All burns are considered sufficiently severe to warrant initial debridement in theatre. Patients undergoing conventional and Biobrane treatment are assumed to require 20 minutes theatre time at the start of treatment, while those treated with ReCell will require 30 minutes theatre time. This is based on feedback from our clinical advisors
4. All patient will remain as inpatients until day 2, following which those fit for discharge will receive re-dressings either as outpatients or as ambulant visitors to the ward. This is based on feedback from our clinical advisors
5. All patients are assumed to be managed either on a general burns ward or in outpatients, if they have been discharged. ITU treatment has been excluded, as its very high costs (£4,210 per day) would obscure other treatment cost differences.

9.1.6 Define what the model’s health states are intended to capture.

As we adopted a decision tree approach, rather than a Markov model, the term “health states” does not strictly apply. However, our model distinguished between the following three mutually exclusive binary states:

- Inpatient treatment vs outpatient treatment
- Requirement for SSG at 10 days vs no requirement for SSG
- Wound 100% epithelialised vs incomplete healing

Each of these three states are associated with different probabilities, according to the treatment method adopted, and each is also associated with cost differences, thereby driving the conclusions of the model.

9.1.7 Describe any key features of the cost model not previously reported. A suggested format is presented below.

Table C4 Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	21 days	The model explores the acute treatment process of burns management, which ends with complete re-epithelialisation. Clinical trials of conventional dressings yield typical times to re-epithelialisation in patients not requiring graft of 13.4 – 18.3 days in patients with the size of burn we are considering. The IBID (3) has documented the mean length of stay for burns in the UK. For the categories Moderate-severe, which correspond to our population of interest, mean length of stay ranged from 8.8 days – 15.3 days. 21 days was therefore considered sufficient to capture the majority of patients and further costs were cut off at this point	Caruso 2006 ³⁰ Silverstein 2011 ³¹ Fong 2005 ³² Cuttle 2012 ³⁸ IBID 2007 ³
Discount of 3.5% for	No discounting applied	The time horizon was too short to justify discounting	

costs			
Perspective (NHS/PSS)	NHS	All the costs accounted for were directly incurred by the NHS hospital trust, with no consideration given to indirect or societal costs. This is in accordance with the scope	
Cycle length	n/a	A Markov model was not used, as a simple decision tree structure allowed as to answer the decision problem adequately. Cycle length is therefore not relevant.	
NHS, National Health Service; PSS, Personal Social Services			

9.2 *Clinical parameters and variables*

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical evidence section of the submission (section 7). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

9.2.1 Describe how the data from the clinical evidence were used in the cost analysis.

Detailed objective data relating to the parameters used in the model are relatively difficult to ascertain, owing to the scarcity of comparative studies in the evidence base. We have used data from both the clinical and costing studies identified in our systematic reviews, in addition to input from four consultant burns surgeons experienced in the use of both ReCell and Biobrane (see paragraph 9.2.5).

Healing times for different treatment modalities. The baseline for these estimates was the expected time to achieve re-epithelialisation using conventional dressings. We identified two studies from our economic review that compared different forms of conventional dressings in patients with burns and a mean TBSA of 5-10%, and provided estimates of the mean time to 100% re-epithelialisation (Caruso 2006³⁰ and Silverstein 2011³¹). One additional similar study (Cuttle 2007³⁸) was identified in the original economic literature search but was excluded from the final results as it did not provide

individual patient level costing data. The six values described in the treatment arms of this study were 16 days, 17 days, 13 days, 17 days, 15 days and 18 days. On his basis, a value of 15 days for time to healing was used..

The impact of ReCell, Biobrane or their combination on these healing rates is not clearly documented in the published literature. In the RCT carried out by Wood et al⁸, the median healing time with both Biobrane and ReCell + Biobrane was 16 days, compared with 36.5 days for conventional dressings, representing a 56% reduction. To eliminate outliers, if we look at the interquadrantic range, at the lower quartile the times to healing were 18.5 days, 14.25 days and 11.5 days for Conventional, Biobrane and Biobrane + ReCell respectively, representing reductions of 23% for Biobrane alone and 38% for ReCell + Biobrane. For the upper quadrant, the equivalent times to healing were 47.7 days, 23 days and 18 days, representing reductions of 52% for Biobrane alone and 62% for ReCell + Biobrane.

Another case series described the use of ReCell alone on SSG donor sites (Echlin 2012a¹³. Although not identical to a thermal burn, the presence of de-epithelialised skin represents a good model for observing healing. Two patients had more than one donor site. In these, the use of ReCell was associated with faster healing than the use of conventional dressings. In one case, the ReCell treated site healed within 7 days, while the conventionally treated site took 36 days (80% reduction). In the second case, the ReCell treated site healed in 13 days, while the conventionally treated site took 20 days (35% reduction).

None of these data are sufficiently robust to generate robust estimates of the impact on healing times. As a conservative estimate, we set baseline healing rate reduction for Biobrane and ReCell alone at 30% with the combination of the two at 40%, while testing across the range 0%-50% for all three.

Requirement to be treated as an in-patient

The possibility of discharge and management as an out-patient hinges on a number of factors:

- Extent of dressings and therefore practicality of home management
- Pain associated with dressing change and therefore requirement for analgesia
- Co-existing conditions/injuries with requirement for inpatient management
- Social and geographical issues

A key difference between conventional dressings and ReCell or Biobrane is the type of dressing required. For ReCell and Biobrane, the wound surface itself remains covered, while secondary dressings – largely required to absorb any excess exudate – is all that needs to be changed. This is relatively simple and pain free. For conventional dressings, the exposure of the wound site not only requires more sophisticated sterile dressing facilities but also tends to be associated with considerably more pain. For these reasons, a patient with conventional dressings is more likely to require in-patient management.

We have been unable to identify any clinical studies characterising this difference so, based on advisor input, have adopted arbitrary values of 50% in-patient care for conventional dressings, with 25% for the other modalities.

Probability of requiring skin grafting

An assessment of the burn is made at around 10-12 days. If at this stage there is evidence of areas of full thickness burn and if, in the clinician's opinion, it is felt unlikely that the wound will be fully healed by secondary intention by 21 days - the critical time for achieving a good scar result (Deitch 1983¹) – then a decision will be made to undertake skin grafting.

We identified data from four clinical trials of conventional dressings with regard to this outcome - two from the economic review ((Caruso 200630, Silverstein 201131) and two from the original search that were excluded on grounds of inadequate costing data (Cuttle 200738 and Ostlie 2012³⁹). The

proportion of patients failing to heal within 21 days in the eight conventional dressing arms in these studies were: 15%, 22%, 26%, 26%, 32%, 34%, 36% and 40%. Based on these results, we chose a baseline value for the model of 30%.

There are very limited equivalent data for the three comparators. The study of Wood et al⁸ selected a group of patients who were felt likely to need surgery from the outset. Of these, 3/4 treated conventionally went on to grafting, 1/4 treated with Biobrane and 0/4 treated with ReCell + Biobrane. Given the small sample and the inclusion criterion mentioned above, it was felt unlikely that these results could be extrapolated, so we sought the opinion of our expert advisors.

They felt that, although Biobrane allowed the speed of healing to be accelerated, there was no evidence that it would have an impact on the likelihood of an SSG being required. For this arm, therefore, no alteration was made to the baseline assumption. For ReCell-treated patients (with or without Biobrane), it was felt that the risk of requiring SSG was substantially lower, with estimates ranging from <5% at one extreme, to a 25-50% reduction compared to conventional at the other. For the purposes of the baseline model, we used an absolute grafting rate of 10% for both ReCell alone and ReCell + Biobrane, with a broad range explored in the sensitivity analysis.

9.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

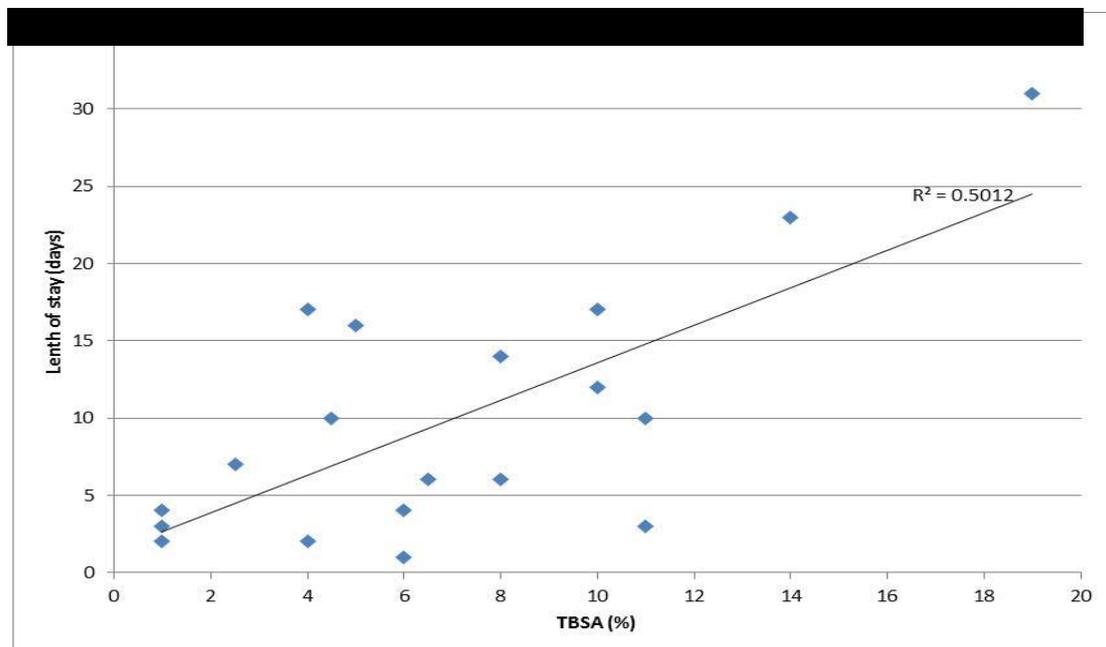
No extrapolation beyond acute phase

9.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

No intermediate outcomes used in the baseline model.

For the sensitivity analysis, the effect of varying TBSA affected was explored. TBSA is closely correlated to overall admission cost (Ahn 2012³⁶, Rawlins 2013³⁷). This reflects its association with a number of cost variables in our model, including the proportion of patients treated as an in-patient, the proportion of patients requiring CCG and the mean time to healing. We have no detailed data available to map these associations accurately. However, the data in the unpublished Rawlins analysis, allow the exploration of the relationship between TBSA and length of stay. – which is, itself dependent on the same three variables. This demonstrates an approximately linear relationship between the two variables ($R^2=0.5$), once outliers have been removed (see figure 6). Within the range of TBSA explored, therefore, we applied a linear correction to the values for inpatient care, total healing time and requirement for SSG, subject certain limits of clinical plausibility:

- Proportion in-patient: 10% - 75%.
- Proportion needing SSG: 5% - 50%
- Mean time to heal: 7 days – 28 days



9.2.4 Were adverse events such as those described in section 7.7 included in the cost analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

Adverse events were not captured in the model, as there is no evidence that the adverse event rates differ between the treatments used.

9.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

The panel of expert advisers was selected by the manufacturer, on the basis that they were consultant burns/plastics surgeons,, with experience of using ReCell, Biobrane and/or the combination in the type of patients included in the scope.

Five consultants were asked to assist and four provided responses to our questions. Each set of responses was independent of the others, with no intention to arrive at a consensus view. This was to ensure that we were able to grasp the range of opinion for each variable, rather than a single compromise value.

Those participating were:

Mr Jeremy Rawlins – formerly Consultant Plastic Surgeon at the Burns Unit at Pinderfields Hospital, Wakefield UK, now working in the same role at the Royal Perth Hospital, Perth, Australia.

Mr Bruce Philips – Consultant Plastic Surgeon at the St Andrews Centre for Plastic Surgery and Burns at Broomfield Hospital, Chelmsford UK

Miss Isabel Jones – Consultant Plastic Surgeon and Head of the Burns Unit, Chelsea and Westminster Hospital, London UK

Prof Fiona Wood – Head of the Burns Unit at the Royal Perth Hospital, Perth, Australia.

Fiona Wood invented and patented the technology that underlies the ReCell system and has a financial stake in the parent company that owns the patents. She also has more experience in the use of ReCell than anyone else in the world, so her advice was considered essential.

The other three advisors have no financial conflicts of interest.

The background information provided included a summary of the NICE scope and the proposed strategy for economic modelling. The clinical background was familiar to all participants, much of it having been generated in their own units.

Each participant was then given a questionnaire to complete, asking for their views on the most plausible care pathways, transition probabilities and treatment durations for each of the nodes in the baseline model. Opportunity was given for extended comments to explain the context and rationale for their responses.

In addition, a series of more generic questions were posed, in order to understand the clinical decision making process insofar as it relates to the factors determining the choice of treatment for any given situation.

The responses were returned to the health economics team, who then had the opportunity to send follow-up questions to clarify their answers. No formal Delphic process was used and advisors were not aware of each other's responses.

9.2.6 Summarise all the variables included in the cost analysis. Provide cross-references to other parts of the submission. A suggested format is provided in table C5 below.

Table C5 Summary of variables applied in the cost model

Variable + name used in model	Value	Range	Source
Proportion of patients treated as an in-patient			
Conventional (pInpatientConv)	50%	25% - 75%	Expert panel opinion
ReCell (pInpatientRC)	25%	25% - 75%	
Biobrane (pInpatientBio)	25%	25% - 75%	
ReCell + Biobrane (pInpatientComb)	25%	25% - 75%	
Proportion of patients progressing to SSG			
Conventional (pSSGConv)	30%	15%-40%	Based on the range of values seen in four comparative studies: Caruso ³⁰ , Siverstein ³¹ , Cuttle ³⁸ and Ostlie ³⁹ . Rationale described in 9.2.1
ReCell (pSSGRC)	10%	5%-20%	Expert panel opinion
Biobrane (pSSGBio)	30%	15%-40%	
ReCell + Biobrane (pSSGComb)	10%	5%-20%	
Mean time to 100% re-epithelialisation			
Conventional (tHealConv)	15 days	13-18 days	Based on the range of values seen in three comparative studies: Caruso ³⁰ , Siverstein ³¹ , and Cuttle ³⁸ . Rationale described in 9.2.1

ReCell (tHealRC)	10.5 days	7.5 – 15 days	Calculated by applying a fixed percentage improvement in healing times to the range of baseline values for conventional treatment. Based on Wood ⁸ and Echlin ¹³ . Rationale described in 9.2.1
Biobrane (tHealBio)	10.5 days	7.5 – 15 days	
ReCell + Biobrane (tHealComb)	9 days	7.5 – 15 days	
Costs of resources.			
Conventional dressing change(cDressing)	£166	£83-249 (+/- 50%)	Pinderfields Burns Unit cost analysis (Rawlins ³⁷)
ReCell (cReCell)	£950 per 320 sq cm treated	Fixed	
Biobrane (cBiobrane)	£60.80 per 320 sq cm treated	Fixed	
Secondary dressing change (cDressminor)	£25	£12.50-£37.50 (+/- 50%)	Nominal cost based on an assumption of 30 minutes nurse time + consumables
Daily bed cost in burn unit (cBed)	£152 (standard burns unit bed)	£76-£228	Pinderfields Burns Unit cost analysis (Rawlins ³⁷)
Daily staff cost in burn unit (cStaff)	£469 (all professionals involved)	£234.50 - £703.50 (+/-50%)	Pinderfields Burns Unit cost analysis (Rawlins ³⁷)
Hourly cost of theatre time (cTheatre)	£5,411 (per hour of use)	£643.50 - £5,500	Baseline value from Pinderfields Burns Unit cost analysis (Rawlins 37). Other UK studies have shown hourly costs ranging from £643.50 (Pellat ³³) to £5,500 (Hemington-Gorse ³⁴). The range tested therefore extends to these limits.
Overall cost of SSG – procedure + post-op care (cGraft)	£5,214.50	£1,948 - £6,663.50	Based on 30 minutes theatre time, discharge at 4 days, secondary re-dressing every 2

			days (all expert advice) + fully healed by 11 days (Ostlie ³⁹). Range tested defined by upper and lower limits of these values for conventional treatment.
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9.3 *Resource identification, measurement and valuation*

NHS costs

9.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

Acute in-patient burns management is specifically excluded from PbR. For this reason there are no burns-specific codes in HRGv4. Pricing is therefore negotiated on a local basis according to a range of formulas. These contracts are not based on individual patient costings and, as such, often differ significantly from the actual costs incurred.

9.3.2 State the Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS) codes for the operations, procedures and interventions relevant to the use of the technology for the clinical management of the condition.

As explained above, OPCS procedure codes are not relevant to this analysis

Resource identification, measurement and valuation studies

9.3.3 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.

The search strategy we used in section 8 captured studies of NHS resource utilisation within its search terms. We reviewed the original search results to identify any additional studies that might have been excluded as part of the original review. This left four relevant studies examining resource use within the NHS:

- Pellat 2010³³ - costing of a major paediatric burn
- Hemington-Gorse 2008³⁴ – cost of running the Welsh Burns Service

- Griffiths 2006³⁵ – cost of a hot drink scald
- Rawlins 2013³⁷ – cost of a mixed caseload of burns

9.3.4 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model¹.

Clinical advisors not formally used to validate costs and resource use, although one of our advisors (Mr Jeremy Rawlins) had carried out one of the analyses and answered specific queries if required.

Technology and comparators' costs

9.3.5 Provide the list price for the technology.

£950 per pack, each of which can treat up to 320 sq cm.

9.3.6 If the list price is not used in the de novo cost model, provide the alternative price and a justification.

n/a

9.3.7 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost model. A suggested format is provided in tables C6 and C7. Table C7 should only be completed when the most relevant UK comparator for the cost analysis refers to another technology.

When completing tables C6 and C7 the price of the technology should refer to the list price stated in 9.3.4 unless a justification for using an alternative price has been provided in 9.3.5. If a technology is not for single use and consumables are needed to provide a treatment, these must be itemised and a breakdown of prices presented.

For all costs presented a source of the data must be stated.

¹ Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Table C6 Costs per treatment/patient associated with the technology in the cost model

Items	Value	Source
Price of the technology per treatment/patient	£950 per 320 sq cm. £1900 for the base case 640 sq cm	Manufacturer
Consumables (if applicable)	Self contained kit – no additional consumables required	
Maintenance cost	None	
Training cost	None (provided by manufacturer)	
Other costs	Use of ReCell adds approximately 10 minutes to the baseline 20 minutes procedure time. This is separately accounted for in the model and is estimated at £901. Renewal of secondary dressing on alternate days costed at £25 – based on 10 days treatment, total cost is £125	Expert opinion
Total cost per treatment/patient	Based on 640 sq cm, total cost is £2,926	

Table C7a Costs per treatment/patient associated with the comparator technology in the cost model (Conventional treatment)

Items	Value	Source
Cost of the comparator per treatment/patient	The cost of initial dressing is absorbed in the theatre cost.	Rawlins 2013 ³⁷
Consumables (if applicable)	n/a (absorbed in dressing cost)	
Maintenance cost	n/a	
Training cost	n/a	
Other costs	Redressings required every 2 days at a cost of £166. Based on 10 days stay, total cost is £830	Rawlins 2013 ³⁷
Total cost per treatment/patient	£830	

Table C7b Costs per treatment/patient associated with the comparator technology in the cost model (Biobrane)

Items	Value	Source
Cost of the comparator per treatment/patient	Prices of Biobrane vary according to dressing size. The mean value is £0.19 per	Manufacturer price list

	sq cm, equating to £121.60 per patient	
Consumables (if applicable)	Standard secondary dressing – absorbed in theatre cost	
Maintenance cost	n/a	
Training cost	n/a	
Other costs	Renewal of secondary dressing on alternate days costed at £25 – based on 10 days treatment, total cost is £125	Expert opinion
Total cost per treatment/patient	£246.60	

Table C7c Costs per treatment/patient associated with the comparator technology in the cost model (ReCell + Biobrane)

Items	Value	Source
Cost of the comparator per treatment/patient	£1900 (ReCell) + £121.60 (Biobrane) for the base case 640 sq cm	Manufacturers
Consumables (if applicable)	No additional consumables required	
Maintenance cost	None	
Training cost	None	
Other costs	Use of ReCell adds approximately 10 minutes to the baseline 20 minutes procedure time. This is separately accounted for in the model and is estimated at £901. Renewal of secondary dressing on alternate days costed at £25 – based on 10 days treatment, total cost is £125	
Total cost per treatment/patient	Based on 640 sq cm, total cost is £3,047.60	

Health-state costs

- 9.3.8 If the cost model presents health states, the costs related to each health state should be presented in table C8. The health states should refer to the states in section 9.1.7. Provide a rationale for the choice of values used in the cost model.

Health states not used in model

Adverse-event costs

- 9.3.9 Complete table C9 with details of the costs associated with each adverse event referred to in 9.2.4 included in the cost model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

No adverse events included in the model

Miscellaneous costs

- 9.3.10 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

No additional miscellaneous costs

- 9.3.11 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

More rapid healing and a better result with regard to pigmentation are likely to result in more aesthetically acceptable scarring. It might be anticipated that this will reduce the long term requirement for restorative surgery. Unfortunately there are currently insufficient data to support this claim, however, so it could not be captured in the model

9.4 *Approach to sensitivity analysis*

Section 9.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

9.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost analysis.

- Multiple univariate deterministic analyses
- Multivariate scenario deterministic analyses

9.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

A deterministic approach was used. Probabilistic sensitivity analyses were not undertaken.

In the field of burns management, individual circumstances determine the course of management to a much greater extent than in many other areas. The data that the model are based on therefore tend to be multimodal and subject to complex, non-normal distributions. This, combined with a lack of rigorous, research-defined data for many of our parameters would make probabilistic analysis essentially meaningless.

For the deterministic ranges, for the same reasons, rather than adopt a mean + 95% CI approach, we have selected either mean +/- 50%, or taken the extremes of estimates available for the parameter in question.

9.4.3 Complete table C10.1, C10.2 and/or C10.3 as appropriate to summarise the variables used in the sensitivity analysis.

Table C10.1 Variables used in one-way scenario-based deterministic sensitivity analysis

Variable	Base-case value	Range of values
Proportion of patients treated as an in-patient		
Conventional (pInpatientConv)	50%	25% - 75%

ReCell (pInpatientRC)	25%	25% - 75%
Biobrane (pInpatientBio)	25%	25% - 75%
ReCell + Biobrane (pInpatientComb)	25%	25% - 75%
Proportion of patients progressing to SSG		
Conventional (pSSGConv)	30%	15%-40%
ReCell (pSSGRC)	10%	5%-20%
Biobrane (pSSGBio)	30%	15%-40%
ReCell + Biobrane (pSSGComb)	10%	5%-20%
Mean time to 100% re-epithelialisation		
Conventional (tHealConv)	15 days	13-18 days
ReCell (tHealRC)	10.5 days	7.5-15 days
Biobrane (tHealBio)	10.5 days	7.5-15 days
ReCell + Biobrane (tHealComb)	9 days	7.5-15 days
Costs of resources.		
Conventional dressing change(cDressing)	£166	£83-249 (+/- 50%)
Secondary dressing change (cDressminor)	£25	£12.50-£37.50 (+/- 50%)
Daily bed cost in burn unit (cBed)	£152 (standard burns unit bed)	£76-£228
Daily staff cost in burn unit (cStaff)	£469 (all professionals involved)	£234.50 - £703.50 (+/- 50%)
Hourly cost of theatre time (cTheatre)	£5,411 (per hour of use)	£643.50 - £5,500
Overall cost of SSG – procedure + post-op care (cGraft)	£5,214.50	£1,948 - £6,663.50

Table C10.2 Variables used in multi-way scenario-based sensitivity analysis. A. Clinical scenarios

Variable	% in-patient	% SSG	Time to heal (days)
Base case	ReCell: 25% ReCell/Bio: 25% Conv: 50% Biobrane: 25%	ReCell: 10% ReCell/Bio: 10% Conv: 30% Biobrane: 30%	ReCell: 10.5 ReCell/Bio: 9.0 Conv: 15 Biobrane: 10.5
TBSA = 320 sq cm	ReCell: 12.5% ReCell/Bio: 12.5% Conv: 25% Biobrane: 12.5%	ReCell: 5% ReCell/Bio: 5% Conv: 15% Biobrane: 15%	ReCell: 7 ReCell/Bio: 7 Conv: 7.5 Biobrane: 7
TBSA = 1,280 sq	ReCell: 50%	ReCell: 20%	ReCell: 21

cm	ReCell/Bio: 50% Conv: 75% Biobrane: 50%	ReCell/Bio: 20% Conventionl: 50% Biobrane: 50%	ReCell/Bio: 18 Conventionl: 28 Biobrane: 21
50% less effect of treatment on all three parameters	ReCell: 37.5% ReCell/Bio: 37.5% Conv: 50% Biobrane: 37.5%	ReCell: 15% ReCell/Bio: 15% Conv: 30% Biobrane: 30%	ReCell: 12.75 ReCell/Bio: 12 Conv: 15 Biobrane: 12.75

Table C10.2 Variables used in multi-way scenario-based sensitivity analysis. B. Cost scenarios

Variable	Bed cost (£)	Staff cost (£)	Theatre cost (£)
Base case	£166	£469	£5411
All costs 25% lower	£124.50	£351.75	£4058.25
All costs 25% higher	£207.50	£586.25	£6763.75

Table C10.3 Variable values used in probabilistic sensitivity analysis

Not carried out

9.4.4 If any parameters or variables listed in section 9.2.6 were omitted from the sensitivity analysis, provide the rationale.

The costs of ReCell and Biobrane were considered fixed, as no reliable data are available regarding the level of discounts available

9.5 Results of de novo cost analysis

Section 9.5 requires the sponsor to report the de novo cost analysis results. These should include the following:

- costs
- disaggregated results such as costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- a tabulation of the mean cost results
- results of the sensitivity analysis.

Base-case analysis

9.5.1 Report the total costs associated with use of the technology and the comparator(s) in the base-case analysis. A suggested format is presented in table C11.

Table C11a Base-case results

Treatment	Total per patient cost (£)
ReCell	£7,891.93
ReCell + Biobrane	£7,787.05
Conventional dressings	£9,542.77
Biobrane	£6,397.82

9.5.2 Report the total difference in costs between the technology and comparator(s).

Table C11b Base-case differences in cost:

Comparison	Difference in costs (£)
ReCell vs Conventional dressings	-£1650.84
ReCell+Biobrane vs Conventional dressings	-£1,755.72
Recell vs Biobrane	£1,494.11
ReCell+Biobrane vs Biobrane	£1,389.23

9.5.3 Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented in table C12.

Table C12a Summary of costs by category of cost per patient (ReCell vs conventional dressings)

Item	Cost <i>ReCell</i>	Cost <i>Conventional dressings</i>	Increment	Absolute increment	% absolute increment
Technology cost	£2,032.62	£1,120.50	£912.12	£912.12	55.3%
Hospital cost	£5,861.31	£8,422.27	-£2,560.96	£2,560.96	155.3%
Mean total cost per patient	£7,893.93	£9,542.77	-£1,648.84	£1,648.84	100.0%

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

NOTE: I HAVE FILLED IN THE % ABSOLUTE INCREMENT COLUMN AS DEFINED IN THE TEMPLATE, ALTHOUGH IN THIS FORMAT THE VALUE OF THIS FIGURE IS UNCLEAR

Table C12b Summary of costs by category of cost per patient (ReCell + Biobrane vs conventional dressings)

Item	Cost <i>ReCell + Biobrane</i>	Cost <i>Conventional dressings</i>	Increment	Absolute increment	% absolute increment
Technology cost	£2,135.33	£1,120.50	£1,014.83	£1,014.83	57.8%
Hospital cost	£5,651.72	£8,422.27	-£2,770.55	£2,770.55	157.8%
Mean total cost per patient	£7,787.05	£9,542.77	-£1,755.72	£1,755.72	100.0%

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table C12c Summary of costs by category of cost per patient (ReCell vs Biobrane)

Item	Cost <i>ReCell</i>	Cost <i>Biobrane</i>	Increment	Absolute increment	% absolute increment
Technology cost	£2,032.62	£250.97	£1,781.65	£1,781.65	119.2%
Hospital cost	£5,861.31	£6,147.85	-£286.54	£286.54	19.2%
Mean total	£7,893.93	£6,398.82	£1,495.11	£1,495.11	100.0%

cost per patient					
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

Table C12d Summary of costs by category of cost per patient (ReCell + Biobrane vs Biobrane)

Item	Cost <i>ReCell + Biobrane</i>	Cost <i>Biobrane</i>	Increment	Absolute increment	% absolute increment
Technology cost	£2,135.33	£250.97	119.2%	£1,884.36	£1,884.36
Hospital cost	£5,651.72	£6,147.85	19.2%	-£496.13	£496.13
Mean total cost per patient	£7,787.05	£6,398.82	100.0%	£1,388.23	£1,388.23
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

9.5.4 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented in table C13.

N/A

9.5.5 If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided in table C14.

N/A

Sensitivity analysis results

9.5.6 Present results of deterministic one-way sensitivity analysis of the variables described in table C10.1.

The results of the one-way sensitivity analyses are presented in table C13 below:

**Table C13a – Results of deterministic one way sensitivity analyses
(ReCell)**

Variable	Range tested	Total cost per patient	
		Low	High
Proportion of patients treated as an in-patient	25% - 75%	£7,106.82	£9,205.79
Proportion of patients progressing to SSG	5% - 20%	£7,596.84	£8,488.12
Mean time to 100% re-epithelialisation	7.5 – 15 days	£7,439.02	£8,571.33
Costs of resources.			
Conventional dressing change(cDressing)	£83 - 249	£7,850.43	£7,933.43
Secondary dressing change (cDressminor)	£12.50 - £37.50	£7,826.62	£7,957.25
Daily bed cost in burn unit (cBed)	£76 - £228	£7,550.98	£8,236.88
Daily staff cost in burn unit (cStaff)	£234.50 - £703.50	£6,835.75	£8,952.11
Hourly cost of theatre time (cTheatre)	£643.50 - £5,500	£5,271.81	£7,942.88
Overall cost of SSG – procedure + post-op care (cGraft)	£1,948 - £6,663.50	£7,486.78	£7,958.33

**Table C13b – Results of deterministic one way sensitivity analyses
(ReCell + Biobrane)**

Variable	Range tested	Total cost per patient	
		Low	High
Proportion of patients treated as an in-patient	25% - 75%	£7,125.69	£8,889.33
Proportion of patients progressing to SSG	5% - 20%	£7,478.32	£8,404.53
Mean time to 100% re-epithelialisation	7.5 – 15 days	£7,561.62	£8,692.93
Costs of resources.			
Conventional dressing change(cDressing)	£83 - 249	£7,745.55	£7,828.55
Secondary dressing change (cDressminor)	£12.50 - £37.50	£7,730.20	£7,843.94
Daily bed cost in burn unit (cBed)	£76 - £228	£7,469.75	£8,104.36
Daily staff cost in burn unit (cStaff)	£234.50 - £703.50	£6,808.02	£8,766.09
Hourly cost of theatre time (cTheatre)	£643.50 - £5,500	£5,164.93	£7,836.01
Overall cost of SSG – procedure + post-op care (cGraft)	£1,948 - £6,663.50	£7,379.91	£7,851.45

**Table C13c – Results of deterministic one way sensitivity analyses
(Conventional)**

Variable	Range tested	Total cost per patient	
		Low	High
Proportion of patients treated as an in-patient	25% - 75%	£7,757.39	£11,328.14
Proportion of patients progressing to SSG	5% - 20%	£8,872.72	£9,989.47
Mean time to 100% re-epithelialisation	7.5 – 15 days	£8,991.87	£10,369.12
Costs of resources.			
Conventional dressing change(cDressing)	£83 - 249	£8,858.02	£10,227.52
Secondary dressing change (cDressminor)	£12.50 - £37.50	£9,542.77	£9,542.77
Daily bed cost in burn unit (cBed)	£76 - £228	£8,862.57	£10,222.97
Daily staff cost in burn unit (cStaff)	£234.50 - £703.50	£7,443.99	£11,641.54
Hourly cost of theatre time (cTheatre)	£643.50 - £5,500	£7,238.47	£9,585.78
Overall cost of SSG – procedure + post-op care (cGraft)	£1,948 - £6,663.50	£8,321.32	£9,735.97

**Table C13d – Results of deterministic one way sensitivity analyses
(Biobrane)**

Variable	Range tested	Total cost per patient	
		Low	High
Proportion of patients treated as an in-patient	25% - 75%	£5,621.02	£7,695.16
Proportion of patients progressing to SSG	5% - 20%	£5,507.54	£6,993.01
Mean time to 100% re-epithelialisation	7.5 – 15 days	£6,046.55	£6,927.24
Costs of resources.			
Conventional dressing change(cDressing)	£83 - 249	£6,274.32	£6,523.32
Secondary dressing change (cDressminor)	£12.50 - £37.50	£6,334.14	£6,463.51
Daily bed cost in burn unit (cBed)	£76 - £228	£5,996.97	£6,800.67
Daily staff cost in burn unit (cStaff)	£234.50 - £703.50	£5,158.01	£7,638.74
Hourly cost of theatre time (cTheatre)	£643.50 - £5,500	£4,094.53	£6,441.84
Overall cost of SSG – procedure + post-op care (cGraft)	£1,948 - £6,663.50	£5,177.37	£6,592.02

9.5.7 Present results of deterministic multi-way scenario sensitivity analysis described in table C10.2.

Table C14 – Results of scenario analyses

Scenario	Total cost per patient				Incremental cost			
	ReCell	ReCell + Biobrane	Conventional	Biobrane	ReCell vs Conventional	ReCell + Biobrane vs Conventional	ReCell vs Biobrane	ReCell + Biobrane vs Biobrane
TBSA = 320 sq cm	£5,537.72	£5,534.37	£5,514.31	£4,491.51	£23.41	£20.06	£1,046.21	£1,042.86
TBSA = 1280 sq cm	£14,402.80	£13,870.80	£16,098.92	£10,684.12	-£1,696.12	-£2,228.12	£3,718.68	£3,186.68
All benefits reduced by 50%	£9,311.99	£9,277.16	£9,542.77	£7,433.46	-£230.78	-£265.61	£1,878.53	£1,843.70
Hospital costs reduced by 25%	£7,595.82	£6,530.71	£7,492.70	£5,060.14	£103.12	-£961.99	£2,535.68	£1,470.57
Hospital costs increased by 25%	£9,185.79	£9,041.36	£11,588.35	£7,734.86	-£2,402.56	-£2,546.99	£1,450.93	£1,306.50

9.5.8 Present results of the probabilistic sensitivity analysis described in table C10.3.

N/A

9.5.9 What were the main findings of each of the sensitivity analyses?

The results of the sensitivity analyses demonstrate considerable robustness in the model, with qualitative comparative results remaining consistent across the ranges tested. None of the univariate analyses revealed areas where parameter variation would have yielded different conclusions.

The scenario analyses demonstrated that the cost difference between ReCell and conventional treatment tended to narrow as TBSA was reduced and if the level of overall benefits or hospital costs were lowered. By contrast, an increase in TBSA or hospital costs tended to widen the gap, with consequent increase in savings

9.5.10 What are the key drivers of the cost results?

- Area of TBSA treated exerted a major effect on all treatments
- Proportion of burns treated as in-patient – this was of particular relevance to conventionally treated patients
- Hospital costs in general, particularly the cost of staff time. The latter had the greatest impact on conventional dressings, while the ReCell results were more sensitive to theatre costs

Miscellaneous results

9.5.11 Describe any additional results that have not been specifically requested in this template. If none, please state.

None

9.6 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 9.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

9.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1 and sections 3.2 and 7.4.4.

No subgroup analyses performed

9.6.2 Define the characteristics of patients in the subgroup(s).

N/A

9.6.3 Describe how the subgroups were included in the cost analysis.

N/A

9.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 9.5.1 (base-case analysis).

N/A

9.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

N/A

9.7 Validation

9.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

Our baseline model explored the management of burns of 640 sq cm. This is approximately equivalent to 5-10% TBSA, depending on the size of the patient. The results yielded overall costs that ranged from £6,398 to £9,543 per patient.

[REDACTED]

[REDACTED] This suggests that our model probably slightly underestimates costs, although the exclusion of complex patients and multiple theatre visits probably accounts for this.

9.8 Interpretation of economic evidence

9.8.1 Are the results from this cost analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

Our literature search identified no other studies that carried out the comparisons identified in the scope. We therefore have no other data against which to benchmark our conclusions.

9.8.2 Is the cost analysis relevant to all groups of patients and NHS settings in England that could potentially use the technology as identified in the scope?

The population chosen had moderately extensive burns (TBSA 5-20%). Although we extended this range to 2.5% - 20% for the purposes of the sensitivity analysis, it would be unsafe to go beyond these boundaries. Smaller burns (<2%) are unlikely to be treated in a hospital setting and, unless there are specific reasons to use it (eg facial burn, visible burn on pigmented skin), ReCell is unlikely to be the treatment of choice.

In patients with more extensive burns, length of stay (and costs) tend rise extremely rapidly. This reflects a number of factors, including a greater likelihood of requiring skin grafting for full thickness injury, greater likelihood of requiring ITU admission, greater likelihood of multiple trips to theatre, the impracticalities of managing a burn of this size as an out-patient. All these factors take the patient out of the scope of this model and, although ReCell undoubtedly has a place in the management plan for these extremely expensive patients, it would require a completely different approach to evaluate its cost impact.

9.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

Strengths:

The model is simple and allows transparent exploration of the cost impacts of various treatments used in acute burns care

Costings are drawn from a recent comprehensive English analysis and are therefore likely to reflect true costs of care for the NICE-influenced population

Sensitivity analysis demonstrates considerable robustness to parameter variation

Weaknesses:

The clinical parameters are based, for the most part, on the results of small studies and case series, or on expert opinion. These estimates are therefore subject to considerable potential error and it has not been possible to generate distributions around the central values

Some of the comparisons made are not necessarily of relevance to normal clinical practice. Biobrane alone, for instance, has its greatest use in patients with smaller or more superficial burns and would less commonly be used in isolation for the types of burns where ReCell might be considered. The apparently lower costs seen with Biobrane alone, therefore, may simply reflect inappropriateness in the comparison

One of the key determinants of burns management is the decision to undertake skin grafting. This depends not primarily on wound size, but depth. Unfortunately there were no data available to incorporate depth in our model, and therefore this element of the analysis may not truly reflect the likely situation. Given that one of the key benefits of ReCell is to reduce the need for (and the size of) skin grafting, we may well have underestimated its benefit.

9.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

With the currently available evidence, there is little opportunity for further modelling in acute burns management. Issues such as the long term impact of ReCell on scar hypertrophy and pigmentation will certainly be worth exploring, once sufficient data become available to support a model.

Appendices

9.9 *Appendix 1: Search strategy for clinical evidence (section 7.1.1)*

Primary search (Burns indication)

9.9.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

All four databases listed above searched

9.9.2 The date on which the search was conducted.

02 August 2013

9.9.3 The date span of the search.

January 1995 – July 2013

9.9.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

MEDLINE/MEDLINE In-Process

Burns [MeSH] OR (Burn* [Textword] OR Scald* [Textword])

AND

ReCell [Textword] OR (Autologous NEAR Cell NEAR Harvest*) [Textwords]

EMBASE

Burns [Subject] OR (Burn* [Textword] OR Scald* [Textword])

AND

ReCell [Textword] OR (Autologous NEAR Cell NEAR Harvest*) [Textwords]

Cochrane Library

Burn* [Title, Abstract, Keywords] OR Scald* [Title, Abstract, Keywords]

AND

ReCell [Title, Abstract, Keywords] OR (Autologous AND Cell AND Harvest*)
[Title, Abstract, Keywords]

9.9.5 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

- Manufacturer database (Avita Medical Ltd). Manual database of known studies held by manufacturer consulted for all studies using ReCell.

- Hand search of abstracts lists for burns-related conferences over the past 5 years: British Burn Association; European Burn Association; American Burn Association; International Society for Burn Injuries.
- Hand search of reference lists from studies identified in the previous searches.

9.9.6 The inclusion and exclusion criteria.

Inclusion criteria:

- Adults and children undergoing treatment for flame burns and scalds
- Treatment with autologous non-cultured skin harvesting (ReCell) used either alone or in combination with other treatments
- Systematic reviews with quantitative outcomes, randomised controlled trials, non-randomised observational studies, comparative or non-comparative case series
- Outcomes including:
 - Speed of healing
 - Number of dressings
 - Length of stay per % TBSA
 - Wound infection rates
 - Scarring: aesthetic and functional outcomes
 - Pigmentation: aesthetic and functional outcomes
 - Re-admission rates for scar management
 - Transfusion rates during skin grafting
 - Number and size of donor sites
 - Growth rate in children
 - Surgical procedure and theatre time
 - Device-related adverse events
 - Analgesic/anaesthetic use
 - Other resource utilisation outcomes not specified above
 - Other patient-relevant outcomes not specified above

Exclusion criteria

- Patients undergoing treatment for indications other than flame burns or scalds
- Treatments not involving autologous non-cultures skin cell harvesting
- Narrative reviews not including quantitative patient effectiveness data, single patient effectiveness data, single patient case reports, animal studies, in vitro studies

9.9.7 The data abstraction strategy.

Four researchers were involved in the process Jonathan Belsey (JB) and Tricia Dixon (TD) from JB Medical Ltd [Sponsor] and Claire Darby (CD) and Andrew Quick (AQ) from Avita Medical Ltd [Manufacturer].

Search results were initially screened to eliminate duplicates. Preliminary assessment of identified abstracts was carried out by two researchers (JB + CD) working together in order to identify clearly excluded studies. Full-text of remaining abstracts were obtained, where available. For data not yet fully published, meeting abstracts/posters were obtained. Draft manuscript obtained from author for one study.

All studies were scrutinised by two researchers independently (JB + TD) to ascertain whether inclusion/exclusion criteria were satisfied. For included studies, quantitative results were extracted by two researchers independently (JB + CD). Data were captured on Excel spreadsheet, although as meta-analysis was deemed not possible, no further data analysis was undertaken. PRISMA diagram constructed on basis of results.

Narrative review of included studies carried out by one researcher (JB) with comments and approval by two further researchers (JB + CD + AQ)

Secondary search (Hypopigmentation indication)

9.9.8 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

All four databases listed above searched

9.9.9 The date on which the search was conducted.

06 August 2013

9.9.10 The date span of the search.

January 1995 – July 2013

9.9.11 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

MEDLINE/MEDLINE In-Process

Hypopigmentation [MeSH] OR Vitiligo [MeSH]

AND

ReCell [Textword] OR (Autologous NEAR Cell NEAR Harvest*) [Textwords]

EMBASE

Hypopigmentation [Subject] OR Vitiligo [Subject]

AND

ReCell [Textword] OR (Autologous NEAR Cell NEAR Harvest*) [Textwords]

Cochrane Library

Hypopigmentation [Title, Abstract, Keywords] OR Vitiligo [Title, Abstract, Keywords]

AND

ReCell [Title, Abstract, Keywords] OR (Autologous AND Cell AND Harvest*) [Title, Abstract, Keywords]

9.9.12 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

- Manufacturer database (Avita Medical Ltd). Manual database of known studies held by manufacturer consulted for all studies using ReCell.
- Hand search of reference lists from studies identified in the previous searches.

9.9.13 The inclusion and exclusion criteria.

Inclusion criteria:

- Adults and children undergoing treatment with ReCell for any reason
- Treatment with autologous non-cultured skin harvesting (ReCell) used either alone or in combination with other treatments
- Systematic reviews with quantitative outcomes, randomised controlled trials, non-randomised observational studies, comparative or non-comparative case series

- Outcomes reported for effect of treatment on pigmentation

Exclusion criteria

- Treatments not involving autologous non-cultures skin cell harvesting
- Narrative reviews not including quantitative patient effectiveness data, single patient effectiveness data, single patient case reports, animal studies, in vitro studies
- Any outcome other than the effect on pigmentation
-

9.9.14 The data abstraction strategy.

Four researchers were involved in the process Jonathan Belsey (JB) and Tricia Dixon (TD) from JB Medical Ltd [Sponsor] and Claire Darby (CD) and Andrew Quick (AQ) from Avita Medical Ltd [Manufacturer].

Search results were initially screened to eliminate duplicates. Preliminary assessment of identified abstracts was carried out by two researchers (JB + CD) working together in order to identify clearly excluded studies. Full-text of remaining abstracts were obtained, where available. For data not yet fully published, meeting abstracts/posters were obtained. Draft manuscript obtained from author for one study.

All studies were scrutinised by two researchers independently (JB + TD) to ascertain whether inclusion/exclusion criteria were satisfied. For included studies, quantitative results were extracted by two researchers independently (JB + CD). Data were captured on Excel spreadsheet, although as meta-analysis was deemed not possible, no further data analysis was undertaken. PRISMA diagram constructed on basis of results.

Narrative review of included studies carried out by one researcher (JB) with comments and approval by two further researchers (JB + CD + AQ)

**9.10 Appendix 2: Search strategy for adverse events
(section 7.7.1)**

NOTE: AS IT WAS APPARENT THAT THE NUMBER OF STUDIES AVAILABLE WAS LIMITED, IT WAS FELT MORE EFFECTIVE TO INCLUDE ADVERSE EVENTS AS A SPECIFIED OUTCOME WITHIN THE MAIN SEARCH, WITH DATA BEING ISOLATED AT THE EXTRACTION STAGE. NO NEW SEARCH STRATEGY IS THUS REPORTED.

**9.11 Appendix 3: Search strategy for economic evidence
(section 8.1.1)**

The following information should be provided.

9.11.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline + Medline In-Process
- Embase
- NHS EED.

9.11.2 The date on which the search was conducted.

20 August 2013

9.11.3 The date span of the search.

January 2003 – July 2013

- 9.11.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

MEDLINE/MEDLINE In-Process

Burns [MeSH]

AND

Cost Allocation [MeSH] OR Cost Control [MeSH] OR Cost of Illness [MeSH]
OR Cost Benefit Analysis [MeSH] OR Healthcare Costs [MeSH] OR Health
Expenditures [MeSH]

EMBASE

Burns [Subject]

AND

Cost [Subject] OR Cost Benefit Analysis Cost [Subject] OR Cost Control
[Subject] OR Cost Effectiveness Analysis [Subject] OR Cost Minimization
Analysis [Subject] OR Cost of Illness [Subject] OR Cost Utility Analysis
[Subject]

NHS EED

Burn* [Title, Abstract, Keywords] OR Scald* [Title, Abstract, Keywords]

[No further limitations applied, owing to dedicated nature of database]

9.11.5

9.11.6 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Consultation with manufacturers (Avita Medical Ltd) regarding any known cost or economic analyses.

Hand search of reference lists from studies identified in the previous searches.

9.12 *Appendix 4: Resource identification, measurement and valuation (section 9.3.2)*

BASED ON THE LIMITED NUMBER OF PUBLICATIONS IN THE FIELD,
THIS ELEMENT WAS DERIVED FROM THE SAME SEARCH AS IS
DESCRIBED IN APPENDDIX 3 ABOVE

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