The HRA interest in good research conduct

Transparent research

May 2013

Purpose:	**The paper sets out how the HRA will promote transparency in research. That is: registration, publication, dissemination, access to data, access to tissue and informing research participants of study results. The HRA has through a period of consultation with key stakeholders identified the agenda now presented for wider comment.**
Status:	**For information and comment**

Drafting note: for the purpose of this paper the general term 'transparent research' is used to reference:

- Trial registration
- Publication and dissemination of research results
- Access to data
- Access to tissue
- Providing information to participants at the end of the study

One action within these proposals is to define standards for what is meant more specifically by each of these terms.

Janet Wisely, HRA Chief Executive

Summary of proposals

The HRA will:

- Lead and coordinate activity in the UK to model and support success, create a culture of openness, challenge behaviours and opinions that present barriers to transparency;
- Work to ensure the current consensus on the need to be transparent, and initiatives to take this forward, are transferred into a combined and effective UK-wide framework to deliver it for health research;
- Take practical steps to promote transparency [early deliverables], including:
    - making registration of clinical trials a condition of a favourable ethical opinion
    - including guidance in participant information sheets and consent form content to ensure consent is not a later barrier to data sharing and future access to tissue
    - strengthen the Research Ethics Committee (REC) review of researcher intentions to make findings, data and tissue available by including this assessment in the current pilot of the ethics officer before REC review
    - provide support and guidance to researchers in implementing new requirements;
- Work with others to consider the UK response in a global setting;
- Continue the REC audit [current work] and consider how we can gather further evidence on the transparency of research in the UK;
- Work with research funders and sponsors to set standards for publication, dissemination and access to data and tissue;
- Continue work through the HRA public involvement steering group to set standards and develop guidance on how participants should be informed of the outcome of study findings [extends current work];
- Commission further work to examine how the HRA can promote greater access to tissue at the end of a research study, and access to tissue held in approved tissue banks [extends current work];
- To explore other suggestions to improve transparency, including:
    - a HRA role to provide a route to maintain a track record of transparency for individuals, funders and sponsors
    - tackling unhelpful perceptions, including that ‘negative’ findings from well designed and conducted studies are less important than ‘positive’ findings
    - working with others, including the General Medical Council, to consider sanctions where there are concerns that failure to publish may constitute professional misconduct
    - clarifying how early release of data sits with later peer reviewed publication, and agreeing sensible frameworks with publishers to dispel fears that early release will prevent subsequent publication
    - encouraging adoption of the Integrated Research Application System (IRAS) number and structured study titles so studies are readily identifiable [current work]

The HRA will develop project plans by end June 2013

The HRA proposals in more detail

Background and introduction

Transparency in relation to publication of research findings, use of patient data and tissue has been the subject of considerable debate for several years. In recent months, the Science and Technology Committee (Commons) Enquiry into Clinical Trials has heard evidence from major research funders, pharmaceutical industry and Ben Goldacre, who has campaigned for the publication of clinical trial data on the AllTrials website. In July 2012, the European Commission produced proposals to revise the Clinical Trials Directive. These developments, and the establishment of the HRA, have led to calls for the HRA to lead in defining a set of proposals to improve transparency in health research.

In taking up this challenge, Janet Wisely the HRA Chief Executive had a series of meetings with key individuals, including representatives of publishers, funding bodies and industry. This work, along with evidence from a survey of Research Ethics Committees, informed a position paper that was discussed at an HRA-hosted workshop on 25 April 2013. Workshop attendees included representatives from industry, research finding bodies, and experts in public and patient engagement. We believe this set of proposals on which we are seeing comments, if implemented will increase public confidence by making the best possible use of their contribution to health research. Increasing transparency will avoid duplication, streamline research by improving efficiency, fundamentally improve patient safety and help to make the UK an even more attractive place in which to do good quality research.

The Health Research Authority (HRA) is responsible for protecting and promoting the interests of patients and the public in health research. The HRA business plan is at http://www.hra.nhs.uk/hra-publications/?entryid85=150764&p=2. The HRA annual report and annual review will be available shortly on the HRA website.

The HRA is committed to a transparency agenda and seeks to improve public confidence in research in the UK. The HRA has an interest in good research conduct and recognises the particular importance of transparency in research. The HRA has signed up to the AllTrials campaign.

The HRA has an opportunity to define a national role that will complement the role of other key stakeholders, and to ensure that patients' interests are protected in health research. The HRA secured funding from ScienceWise and has undertaken an extensive programme of public dialogue and patient involvement that has also informed these proposals. This work will be published shortly on the HRA website.

Transparent research – the HRA agenda

The HRA has an established role to promote transparency, largely through RECs and the publication of research summaries. The HRA recognises it has two distinct roles, one to identify and deliver specific actions for the HRA and the other to lead where actions may also sit with others. An essential component of working with others was taking the time to set out the agenda in collaboration to ensure those with whom solutions sit have had time to contribute and

shape this important agenda. The details of the workshop held on 25 April are included in *Appendix 1*.

Application to a REC

Applicants to RECs are asked to register trials and plans for publication and dissemination are submitted to the REC. Applicants are asked about plans to make data and tissue available at the end of the study, and how the researcher expects to inform research participants.

A challenge for the HRA is that at the time of ethical approval all elements, including registration, will be about plans. Whilst the HRA supports the views of others that researchers should register trials early, given the high volume of provisional opinions by RECs and subsequent changes that may be made to study design registration too early would not be advisable. Potentially, the HRA could make the registration of a trial a condition within a provisional opinion but this would mean that every study would get a provisional opinion and need to come back for a final approval before it could start. This would be an unreasonable burden and the HRA's vision is to make it easier to do good quality research in the UK. However, there are options to make registration a condition of the REC approval, and a decision option for RECs is to place additional conditions on the favourable opinion.

A second challenge is the wide range of studies that are reviewed by NHS RECs within the research governance framework for research in the UK. Registration may not be suitable for all studies reviewed by RECs (NHS RECs review studies of educational value, as well as health services research and clinical trials) and registration cannot therefore be a simple condition of ethical approval for all. Similarly, what is appropriate in terms of publication, dissemination and access to data or tissue may be different for individual studies, and a simple one size fits all approach is not likely to be successful.

The HRA issued (January 2013) a 'Shared Ethical Debate' to RECs in the UK asking for views on how they currently review plans to ensure transparent research. If we are to pay greater attention to monitoring compliance with these plans, that are effectively conditions of the favourable ethical opinion, we need to pay greater attention to what we approve and identify early potential barriers that may benefit from a management strategy, e.g. identifying potential conflicts of interest and how they may be managed. The document issued to RECs and headline results are included at *Appendix 2*.

Proposal:

- The HRA will make trial registration for clinical trials a condition of REC approval from September 2013. The HRA will consider and agree which categories on studies on the IRAS (Integrated Research Application System) will fall within the condition, and also agree a reasonable timeframe for the registration as part of the condition. Clinical trials are studies with any clinical intervention, including drug trials.
- The HRA will work with funders to agree what we mean by publication and dissemination, to set common definitions and standards for different categories of studies, and in consideration of different audiences – public, participants, funders, regulators, researchers and clinicians.

- The HRA will include the consideration of plans for publication, dissemination, and access to data and tissue within the current ethics officer pilot (details of this pilot are in the HRA business plan) and develop a framework that will categorise studies according to the potential impact results may have on patient care. A draft framework for this review is included in *Appendix 3.*

Monitoring compliance with approval conditions

The HRA has started to audit mechanisms to identify compliance with these approved plans, based on a review of the final report and setting up prompts to follow up where plans are not yet complete. Initial results show, as expected, that the majority of final reports to RECs are ahead of publication and that it is a labour intensive task to look through final reports when little evidence can be gained. There are potentially other simple mechanisms, asking specifically in a routine letter for evidence 6 months after the final report and also looking at opportunities for a higher level sponsor of funder assurance so the number of individual project assurances is less. The HRA expects to be able to identify mechanisms to judge compliance.

Proposal:

- The HRA will look for further mechanisms to monitor compliance with the agreed conditions of REC approval.

Gathering further evidence

There is some evidence on publication rates, for example the NIHR (National Institute for Health Research) and MRC (Medical Research Council) as funders have data to show very high rates of publication for studies they fund. There is not a full picture though across all studies.

Proposal:

- The HRA will continue the current REC audit and also explore other opportunities for getting evidence of publication in the UK.

Research conduct

The HRA, through the operational arm of the National Research Ethics Service, manages reported potential breaches or misconduct. The HRA has no powers to investigate, but we can require others to do so and seek reassurances. The role is described in more detail in *Appendix 4*, a high-level summary of reported potential breaches or potential misconduct is provided in *Appendix 5*, and the relevant NRES SOPs are in *Appendix 6*.

Proposals:

- The HRA will explore mechanisms for how it may keep a register to show compliance and to enable RECs and others to be assured through this where applicants, funders and sponsors can demonstrate such good conduct.

- The HRA recognises that deliberate failure to publish is research misconduct and will work with others, including the General Medical Council, to agree how sanctions may be applied.

Consent

There is concern that consent now may prevent further data sharing later:

Proposal:

- The HRA will include advice and recommended text in consent forms to ensure that any barriers to future data sharing and access to tissue are avoided by ensuring consent is in place at the outset.

Future access to tissue

The application to a REC also asks about plans to make tissue available for future studies at the end of a research study and for tissue held in approved tissue banks. The HRA recognises this is also an important issue.

Proposal:

- The HRA will commission further work to look at access to tissue, working closely with the HTA and others.

Study titles and the IRAS identifier

The HRA is currently seeking views on proposals to adopt a unique structured study title, and wider use of the IRAS number so that it is possible to track and monitor studies in the UK from funding through to publication. Details are provided in *Appendix 7*.

Proposal:

- The HRA will continue to promote the wider use of the IRAS number and structured study titles.

Informing research participants of the outcome of research studies they have participated in

The HRA public engagement work has identified that further work is required to look how we most effectively provide information to participants and to look at the barriers to getting information to potential, current and past research participants. A high level summary of relevant findings is provided in *Appendix 8*, a full report will be published shortly. Further work will consider the provision of information specific to an individual, e.g. what arm of a randomised trial they were in, as well as general access to study findings. The emerging views from the work so far are that participants want findings to be available so that they can access them as they wish. The HRA will work with others to set standards and provide guidance on how information should be provided to participants. Consideration of these plans against agreed

standards will continue to be an issue for the REC to review at approval. This work will continue through the HRA involvement work stream.

The UK and the UK position globally

There is some concern that a more rigorous approach in the UK could be seen to make the UK a less attractive place to do health research. The HRA believes a proportionate approach, that includes consideration by ethics officers at each application will not delay or deter, and will not be detrimental to the UK. The HRA believes there is an opportunity to use a sensible proportionate approach to promote further confidence in health research in the UK to make it a more attractive place to do research, and to improve patient and public confidence in it.

- The HRA will lead work to ensure that the work in the UK is not detrimental, or perceived to be, detrimental to UK competiveness for health research.
- The HRA will use its role to promote transparent research to increase public confidence in research in the UK.
- The HRA will use case studies to support this communication.

Leadership

A key role for the HRA will be to continue to provide leadership in the UK, to support, model and promote success and tackle barriers and perceived barriers to transparency. The HRA will support better understanding of the importance of results from robust studies which do not show statistically significant findings ('negative' results) as well as studies that show statistically significant findings ('positive' results).

- The HRA will continue to work with others to identify issues that are barriers or perceived barriers to transparency, including:
    - tackling unhelpful perceptions, including that negative findings from well-designed and conducted studies are less important than positive findings
    - gaining greater awareness of online journals as an accessible route to publication
    - clarifying how early release of data sits with later peer reviewed publication, and agreeing sensible frameworks with publishers to dispel fears that early release will prevent publication.

The HRA will begin immediately to pull together project plans for the individual elements within these proposals. Some will be a continuation of current work, others will be immediate priorities with early implementation, for example registration of clinical trials as a condition of REC approval, whilst some areas will need further scoping and consideration. A further update on these plans will be issued at the end of June 2013. Further references are included in *Appendix 9*.

Appendix 1

Work undertaken to agree the current HRA position

The HRA held a number of interviews and hosted a small workshop on 25 April 2013 to identify actions for the HRA to promote transparent research and to distinguish where these are direct roles to deliver and areas of work where the HRA is best placed to lead a wider agenda.

Through presentation and discussion:

- to describe current consideration by NHS Research Ethics Committees (RECs)
- to hear about the HRA plans to follow up on declared and approved intentions to register, publish and disseminate research, provide access to data and tissue and inform participants of study results
- to understand the established role of the HRA's National Research Ethics Service (NRES) in managing reported potential cases of fraud and misconduct
- to explore what we mean by publication and dissemination of research results
- to identify issues that may present barriers to making data and tissue available
- to debate key issues to inform a policy framework for the HRA:
    - should a REC ever approve a study that declares it will not disseminate or publish the results of the research and, if not, should dissemination and publication of results be a requirement of a favourable ethical opinion? Should RECs (and funders) require data and tissue to be made available at the end of studies?
    - wilful acts preventing transparency vs barriers to transparency
    - appropriate barriers, e.g. quality issues
- a framework for ethics committees in considering and approving plans for transparent research
- what can / should the HRA or others do if they identify failure to comply with agreed plans for transparency? When would it be appropriate to apply sanctions, and what are the options available? Is self-regulation more likely to be successful?
- how do we ensure better identification of studies so we can monitor compliance to a transparent approach – a linked HRA proposal for universal study title and greater use of the IRAS number as an identifier

Organisations / individuals consulted / attending the workshop on 25 April:

	Surname	Forename	Organisation
1.	Abouzeid	Christiane	Bio Industry
2.	Ashton-Key	Martin	University of Southampton
3.	Bevan	Simon	NETSCC

4.	Bourne	Sue	HRA
5.	Bridge	Daniel	Cancer Research UK
6.	Buckland	Sarah	INVOLVE
7.	Chalmers	Iain	James Lind Library
8.	Davidson	Bill	Department of Health
9.	Denegri	Simon	NIHR
10.	Faure	Helene	Current Controlled Trials
11.	Greenacre	Will	Wellcome Trust
12.	Keen	John	NREA / REC Chair HRA
13.	Kirkbride	Joan	HRA
14.	Meredith	Sarah	MRC CTU
15.	Parry	James	UKRIO
16.	Philpots	Liz	Association of Medical Research Charities
17.	Radway-Bright	Emma	ABPI
18.	Rawle	Frances	Medical Research Council
19.	Rawlins	Mike	AMS
20.	Smith	Tom	HRA
21.	Stevens	Mike	Chief Scientist Office, Scotland
22.	Stewart	Derek	NIHR
23.	Stone	Julie	HRA NED

24.	Taylor	Mark	Chair, HRA Confidentiality Advisory Group
25.	Tebbutt	Steve	HRA
26.	Thakker	Nalin	The University of Manchester / HRA REC
27.	Thomas	Carys	NISCHR
28.	Ward	Martyn	MHRA

Summary notes of workshop

Delegates recognised that publication has more than one meaning. Information is now available in the public domain without being 'published' in a traditional sense. Some of these mediums may not achieve the outcome desired (and this will be different for different audiences). Data does need to be accessible; however, there is also a duty to protect participants, who might ask what benefits have resulted from their participation.

There is a key role for sponsors / funders to define their publishing expectations to researchers from the outset. Indeed some sponsors / funders withhold a percentage of funding until research is lodged with the sponsor/ publications submitted. Also need to be mindful that there are differing levels of research from Master's students to Clinical Trials. There is a duty on the researcher to at least have the intention to publish, appreciating that for commercial reasons, there may be a deferment in all data being available. Would it be reasonable to expect publication of data as long as five years, from completion of research? Consensus that need to apply a timescale that considers potential impact on patient care – whether negative or positive findings but that as long as research is registered longer to making data openly accessible is OK if those considering doing further research know the research has been done and can request the data / results.

'Sanctions' on ethical approval of future applications on the basis of previous non-publication would require further consideration and potentially legal advice. Sanctions for failing to publish according to agreed plans – at least as a deliberate act or by negligence – would need sanctions through established routes – employers and professional bodies.

Identified that HRA has a role in clinical trials to ensure at point of approval that there is an intention to register trial as per declaration of Helsinki, and that making this a condition of the ethical approval is a legitimate and proportionate approach.

The HRA needs to seek to dispel the myth that publication of negative result is less valid than a positive result.

In promoting open data and transparency, there is a need to protect the rights of the individual participant, need to have standardisation on data submissions and ensure that genetic

identification, for example, is safeguarded. Can all of this be undertaken on a UK scale or is there a need for European / worldwide agreement?

Next steps

- UK / Global agenda – who leads? HRA initially?
- HRA – ethics application – Ethics Officers can look at intentions to publish now
- HRA – look for commitment to register all clinical trials
- HRA – work with funders on standards and publication, certainly initially those who are open to such a development
- HRA – consider more evidence of good research conduct
- Consider how to evidence compliance
- HRA – look to make further links to professional bodies, not least GMC
- Broader category – general leadership and collaboration within research
- All – modelling success and increasing awareness

Direction of developments undertaken by the HRA gained significant support

"There is a responsibility to publish high quality research as the HRA and others are leading on",

Iain Chalmers, James Lind Initiative

"Role for HRA is to facilitate this and bring other players together",

Mike Stevens, Chief Scientist Office, Scottish Government

Appendix 2

NHS
Health Research Authority

NRES SHARED ETHICAL DEBATE

"Publication and Dissemination of Research and Research Results"

Conclusion:

By far the majority of RECs (two thirds of those who answered) do, when reviewing applications, actively review and consider the intention to publish, plan to publicly register the research and publish and disseminate the research results. However, the majority of RECs (81% of those who answered) preferred a proportionate approach e.g. applying a higher standard to the conduct of CTIMPs and a less stringent standard to student projects.

The top 3 themes that emerged from the REC responses were:

- Difficulty in monitoring/policing publication
- Difficulty in registering/publishing some types of research (inc. cost of publication)
- Feedback to participants considered important

Many RECs did not feel that it was practical or possible for them to monitor or police whether a study did in fact publish the results. In addition, it was acknowledged that many researchers often experience difficulty in registering (particularly non-CTIMP studies) or publishing some types of research e.g. those with negative results. 10 RECs considered that their primary focus should be on the feedback of results to the participants themselves.

The majority of RECs who responded recognised that publication and dissemination of research results was part of their ethical review. Generally, RECs believed that greater emphasis needed to be placed on this issue so that applicants would be aware that this formed part of the ethical review. Interestingly, of those who made any comment, the majority (75%) didn't see the need

to change the standard NRES approval conditions and those that did felt that there was a need for greater clarity of the existing conditions.

Those who agreed with the proposal that "the HRA seek to endorse voluntary publication schemes" seemed somewhat reluctant or saw it only as an interim measure. Many felt that the HRA should oversee a central database or registry of trials and results. It was unclear if many RECs were aware of the existence of the HRA's research register as only one REC explicitly referred to it.

Whilst many RECs were broadly sympathetic to the reasons behind the proposals made by Ben Goldacre the majority, of those who addressed the issue directly, either rejected them outright or felt that they would be impractical or impossible to implement. For example:

> REC 29: "*Overall the committee felt that the points raised in Supplementary Questions 1 and 2 were good aspirations, and were supportive of them being explored. However, any system would need to be reasonable, fair and enforceable, and there did seem to be several practical difficulties in achieving this"*

In doing so they cited the difficulty of publication and the often lengthy process involved, meaning that the year timeframe for publication was extremely unlikely to be met in practice (26 RECs) and the difficulty in applying the same standard to all types of research (11 RECs). A small number of RECs also felt that the proposals would be unfair to researchers associated with a non-published study but who were not in direct control of its publication. 6 RECs felt that it was not correct to equate a failure to publish with "research misconduct".

17 RECs raised the issue of what we mean by "publication" noting that there were alternative routes available for placing results in the public domain other than the traditional route of publication in a journal.

A significant number of RECs (14) felt that it was not their role to monitor publication and suggested that this was more properly the responsibility of others (sponsors, funders etc).

Debate documentation:

"Publication and Dissemination of Research and Research Results"

As many of you will know, the important issue of open access to research results is currently receiving widespread attention and debate. This is due, in part, to the recent publication of Ben Goldacre's book 'Bad Pharma' in which he makes a number of criticisms aimed at the pharmaceutical industry and regulators, amongst others, regarding the conduct of drug trials and the publication of trial results. He also makes a number of suggestions for how he believes the problems he has identified might be remedied.

The HRA fully supports the registration of research and subsequent publication of research results, and is taking the following steps:

- Development of a policy framework to describe its position and role in ensuring both the publication and dissemination of results, and open access to data and tissue
- Ensuring that greater attention is given to adherence of agreed plans for publication and dissemination of research results by review of the final report and follow up where necessary. A pilot of this work will start in April 2013

In order to support these developments, the HRA now needs to consult with RECs on their role in identifying issues that might prevent the future publication of research results so that appropriate management strategies can be put in place.

Therefore, we invite members to debate the questions listed below at a full REC meeting in either February or March 2013.

Responses to the questions and comments should be provided on this form and returned electronically to hra.qa@nhs.net.

The responses will be analysed and a report produced and circulated to all RECs.

The findings will also inform future work on the development of a framework of questions and considerations regarding the publication and dissemination of research results. A draft of this framework is available from your coordinator if your committee or individual members wish to provide any comments at this stage.

Thank you for taking part in this debate. Your views are very much appreciated.

Name of REC	
Date of Review	

Main Questions for Debate
1. **Does your REC actively review and consider the intention and plans to publicly register the research and publish and disseminate the research results when reviewing applications?**

Are varying standards used when reviewing different types of studies?

2. **What, if anything, should be done to strengthen the conditions of REC approval?** The publication plans, as presented and approved, form part of the favourable ethical opinion, as such, they are a condition of the ethical opinion. Is your REC aware of this condition?

   Should this be made more explicit?

   Should the current approval conditions be revised?

3. **Should the HRA seek to endorse voluntary publication schemes emerging, for example, from industry?**

   On what basis would the HRA do this?

   Is this welcoming enough?

   Or, should the HRA consider and comment on specific aspects?

Supplementary Question

In 'Bad Pharma', Ben Goldacre makes the following suggestions:

1. No trial should be approved without a firm guarantee of publication within one year of completion
2. No person should be allowed to conduct trials in humans if a research project they are responsible for is currently withholding trial data from publication more than one year after completion. Where any researcher on a project has a previous track record of delayed publication of trial data, the ethics committee should be notified, and this should be taken into account, as with any researcher guilty of research misconduct

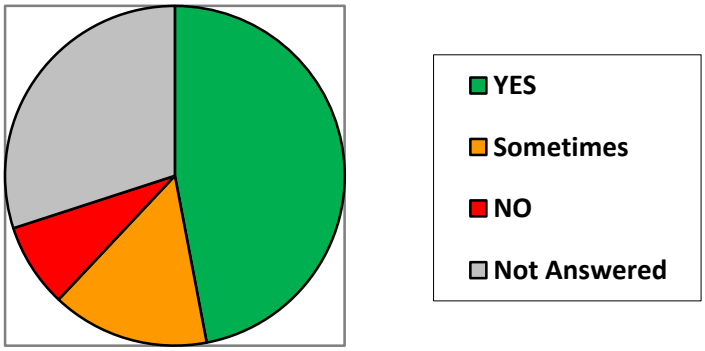
What is your view of these?

Response of REC to main and supplementary questions
Comments on the 'Considerations and Questions' paper available from the REC Coordinator (if reviewed)
REC Comments about the idea of single issue ethical debate
Please let us have your views on single-issue ethical debate as an idea, any way you think it can be improved and any single issues you would like to suggest for debate

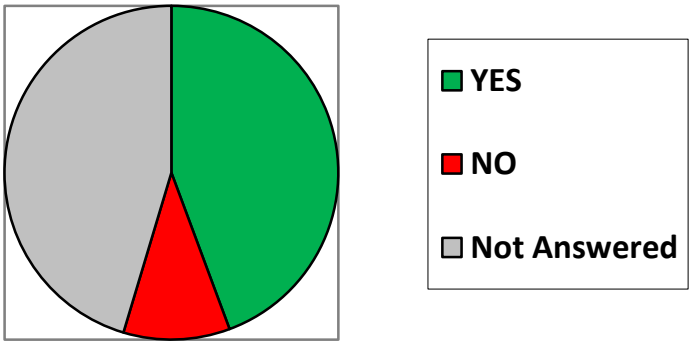
Results:

Q.1 Does your REC actively review and consider the intention and plans to publicly register the research and publish and disseminate the research results when reviewing applications?

Yes	Sometimes	No	Not Answered
47	15	8	30

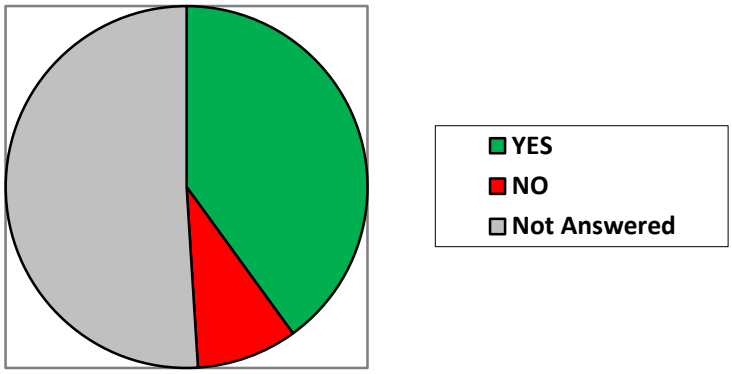


Are varying standards on publication used when reviewing different types of studies?		
Yes (Standard Varies)	**No (Same Standard)**	**Not Answered**
43	10	47



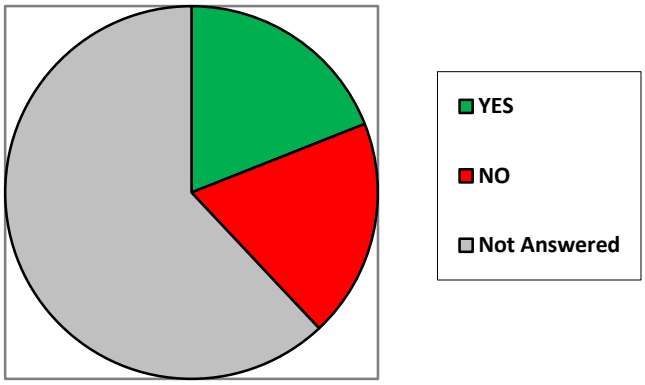
Themes	No. of RECs
Difficulty in monitoring/policing publication	16
Difficulty in registering/publishing some types of research (inc. cost of publication)	13
Feedback to participants considered important	10
Not RECs Role/Not part of ethical review	8
What do we mean by 'publication'/Different ways of publicising research	7
Difficulty in reviewing *intention* to publish	5
Reasons not to publish commercially sensitive results	4
HRA/other body provide national database for registration publication of results	3
Difficulty in finding data even if 'registered' or 'published'	1
IRAS application form should be revised to make requirement clearer	1

Q.2 Is your REC aware of current conditions for favourable opinion? (What, if anything, should be done to strengthen the conditions of REC approval?)		
Yes	**No**	**Not Answered**
40	9	51



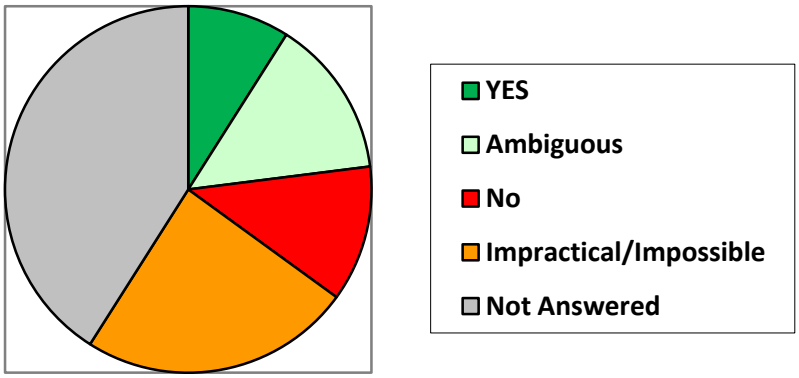
Themes	No. of RECs
Significant monitoring difficulties	27
A need to place greater emphasis on this	25
There is NO need to revise conditions	14
There IS a need to revise conditions	5
NRES/HRA should take a role in monitoring (it's not the role of REC)	13
Use and develop existing processes such as the annual /final report	7
The continuing problem of separating and managing "publication" and "placing research in the public domain"	7
Concern that this may drive research out of the UK	3
Diversity of research makes a uniform position difficult	3
The use a "carrot and stick" approach and the need to separate "serial non-publishers" from those who have tried to publish	2
Publication is not an ethical issue/should not concern RECs or HRA	1

Q. 3 Should the HRA seek to endorse voluntary publication schemes emerging, for example, from industry?		
Yes	**No**	**Not Answered**
19	19	62

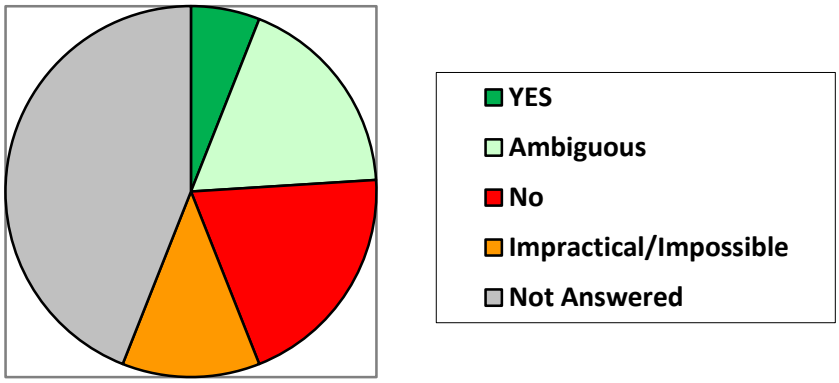


Themes
A voluntary scheme is better than nothing/reluctant acceptance
A voluntary scheme should be regarded as an interim measure
Any scheme needs to be compulsory
HRA should build its own register
Pragmatic concern that given conflicts of interest in this area, a voluntary scheme wouldn't work

Supplementary Q. 1 In 'Bad Pharma', Ben Goldacre makes the following suggestions: **No trial should be approved without a firm guarantee of publication within one year of completion.** **What is your view of this?**				
Yes	**Ambiguous**	**No**	**Impractical/Impossible**	**Not Answered**
9	14	12	24	41



Supplementary Q 2. In 'Bad Pharma', Ben Goldacre makes the following suggestions: **No person should be allowed to conduct trials in humans if a research project they are responsible for is currently withholding trial data from publication more than one year after completion. Where any researcher on a project has a previous track record of delayed publication of trial data, the ethics committee should be notified, and this should be taken into account, as with any researcher guilty of research misconduct** **What is your view of this?**				
Yes	**Ambiguous**	**No**	**Impractical/Impossible**	**Not Answered**
6	18	20	12	44



(NB. The category “Ambiguous” has been used where RECs were broadly in sympathy with the suggestion that appropriate measures need to be put in place but did not finally express a definite view on the acceptability of the proposals)

Themes	**No. of RECs**
Suggestion 1: One year too short/option for extension	26
What do we mean by ‘publication’/Different ways of publicising or disseminating research/Guarantee that results are ‘made public’	17
Not RECs Role/Not part of ethical review/unclear whose role	14
Same standard cannot be set for all studies	11
Publication of results/summary on national database	8
Represents extra barrier to research/Research may move abroad/Extra layer of bureaucracy	7
Unfairly penalises those not responsible for publication	7
Difficulty in publishing some types of research (inc. cost of publication)	6
Failure to publish is not equivalent to ‘research misconduct’	6
Publication of raw data should be encouraged/mandatory	3
Not all research should/needs to be published	2
Distinction between delaying publication and withholding (negative) results	2
Failure to publish is equivalent to ‘research misconduct’	1

Appendix 3

Issues for consideration

REC considerations – at approval – to be included in ethics officer pilot – draft

Issue	**Considerations and recommendations**
Trial registration	There is broad agreement that clinical trials should be registered and that registration should be a condition of the favourable ethical opinion. For other studies, further judgement is required. The HRA will: • consider what categories of studies (as determined by the IRAS filter) for which registration should be a condition of a favourable ethical opinion • consider an appropriate timeline for registration • implement registration for these studies as a condition of the favourable ethical opinion by September 2013 • look at simple no cost registration direct from the new build IRAS system so that registration can become a condition for REC approval for all studies when the new systems go live in late 2014
Publication / dissemination – putting the research results in the public domain	The REC application currently asks about plans for publication and dissemination of research results. There is currently a variable approach by RECs, but broad agreement that there is a role for RECs to consider plans (and timelines) at the outset and apply conditions based on a categorisation of the studies so those with a potentially high impact on patient care are set more rigorous requirements and are monitored more closely. • Include this review into the ethics officer pilot and develop a framework and standards for review of these plans as part of that pilot • Issue framework and standards by end December 2013

Appendix 4

The established NRES role – reported potential fraud and misconduct

The NRES SOPs provide for the REC to review its favourable ethical opinion at any time in the light of safety reports, progress reports or any other information received about the conduct of the study. For non-CTIMP studies, the REC may suspend or terminate the favourable ethical opinion. For CTIMP studies concerns are reported through the MHRA (within the terms of the NRES – MHRA MoU), as the MHRA is the competent authority and may suspend a CTIMP. A summary of the year to date reported potential breaches / potential fraud misconduct is provided in *Appendix 5*. NRES keeps a more detail confidential register of these reports. Many are self-reported and it is important that confidentiality is protected to ensure sponsors and researchers continue to report.

Reports are managed by NRES. NRES has no role to investigate but, as appropriate, it will require an investigation and will expect to see the outcome of such an investigation. Where action is potentially required from the REC, NRES may provide a summary and assessment of the incident for the REC. NRES operations will liaise with the REC that has provided the ethical review and opinion, and a REC may issue a notice of intention to suspend, suspend or terminate the opinion. The NRES experience is that sponsors and employers will respond professionally to such reports, welcome and action the advice provided and, as necessary, will usually address issues immediately or suspend recruitment themselves without the formal action from the REC. NRES will also reference the role of the UKRIO when responding to reports and encourages sponsors or employers to seek advice as required.

A typical sponsor response

A REC was made aware of the use of information and consent forms at one study site that were not as approved by the REC, and that included language that the REC considered inappropriate. The matter was raised and managed through SOPs, the sponsor conducted an immediate investigation and reported back to NRES to advise that the non -NHS site would no longer be used by the sponsor, and that no payment would be made for recruitment with the revised and non-approved information sheets. NRES was content that the sponsor had taken required action and that it was a matter for the employer to deal with any local employment issues for the investigator involved.

The matter for the particular study was resolved and the REC did not withdraw the favourable opinion. The matter was closed on the NRES register.

The HRA research integrity lead, Frank Wells, meets quarterly with Joan Kirkbride to formally review and provide advice on the response to reported breaches or fraud and misconduct. The HRA Board will receive a summary of reports and will, in Part 2 confidential business, review reports that have been classified as major by NRES Operations.

Appendix 5

This is a summary of reported potential breaches / potential fraud misconduct as identified in the role described in Appendix 4 which delivers the standard operating procedure described in Appendix 6.

Breach of GCP/RGF/Potential F&M 1 April 2011 – 31 March 2012

Reported breach classified as:	
Major	4
Minor	7

Type of study:	
CTIMP	8
Non-CTIMP	3

Breach originally identified and notified by:	
Investigator	3
Study Sponsor	7
REC	1
MHRA	0
R&D/Care Organisation	0
Other	0

Breach arose from the actions of:	
Researchers	9
Sponsor	2
Care Organisation	0
REC	0
Other	0

Appendix 6

NRES SOPs – research integrity

Review of a favourable ethical opinion

9.87: The main REC may review its favourable ethical opinion of a study at any time in the light of safety reports, progress reports or any other information received about the conduct of the study. This may include concerns raised by patients, service users, carers or patient organisations, or issues raised by media reports. The Chief Investigator or sponsor may ask the main REC to review its opinion, or seek advice from the REC on any ethical issue relating to the study.

Suspension or termination of opinion on a non-CTIMP

9.88: A favourable ethical opinion on a non-CTIMP may be suspended or terminated by the main REC due to serious concern about the ethical acceptability of the study relating to one or more of the following:

(a) The scientific validity of the study

(b) Risks to the safety or physical or mental integrity of participants

(c) The competence or conduct of the sponsor or investigator(s)

(d) The feasibility of the study

(e) The adequacy of the site or facilities

(f) Suspension or termination of regulatory approval for the study.

9.89: In the case of multi-site studies, the favourable ethical opinion for a particular site may be suspended or terminated by the main REC following new information received from the site-specific assessor or another source about the suitability of the site. The favourable opinion could continue to apply to other trial sites in these circumstances.

9.90: Before suspending or terminating an opinion, the REC should consider whether it is appropriate to first notify the sponsor of the action it intends to take, setting out its concerns in full and giving the sponsor opportunity to address them within a specified timeframe, by issuing a Notice of Intention to Suspend or Terminate a Favourable *REC SOPs - Version 5.0 September 2011* 162. Opinion (NISTFO) (SL42). However, immediate suspension is permitted where the REC judges there would be a serious risk to the health or safety of participants if the study continued in present circumstances.

Study titles and identifiers

The HRA has accepted the recommendations in the paper below and has sought support to take these forward under the remit of the HRA Collaboration and Development Steering Group. The HRA will now proceed to seek wider views on the proposed guidance, how it may be implemented and how this, alongside a wider use of the IRAS number as an identifier, will enable research to be reliably identified in the UK.

The proposals were discussed and agreed at the Collaboration and Development Steering Group on 1 February 2013. Plans to take the next stage forward are currently being agreed.

Developing guidance for the universal format of titles of research projects

DRAFT REPORT and RECOMMENDATIONS as commissioned by the Health Research Authority

Prepared by Hugh Davies, Health Research Authority, and Iveta Simera, EQUATOR Network, Centre for Statistics in Medicine, Oxford, January 2013

Summary

Why we need to improve the quality of titles

Many titles of research projects are not satisfactory. Their style is inconsistent with jargon and abbreviations, and importantly they don't describe the key study elements. This matters. We don't know what's 'in the tin' and the lack of a consistent title that describes the study hinders all aspects of research from design to review, explanation to the public and potential participants, assimilation into the corpus of research knowledge and ultimately subsequent systematic reviews.

To improve the quality of titles of submitted studies, the HRA initiated a project aimed at developing guidance for a universal structured format of study titles. The improved title format will complement adoption of a unique study identifier system to facilitate more reliable identification of studies.

Literature review

The first step in developing guidance on titles was to conduct a systematic literature overview to inform the development of recommendations. The key objective of the review was to

systematically identify and summarise available research analysing various aspects of titles, identify problems associated with suboptimal titles, and summarise the existing guidance for preparing research titles.

We searched major bibliographic databases and online resources of various organisations, including major UK research funders. Most of the identified evidence focuses on titles of journal articles; key issues include misrepresenting the study in the title and use of jargon and abbreviations.

Very limited guidance has been found for producing structured titles. The most advanced system was developed by the Cochrane Collaboration and relates to titles of systematic reviews. None of the major UK funders (MRC, NIHR, Wellcome Trust and Scottish Chief Scientist Office) request structured titles for submitted grant proposals.

Findings of the review support the following recommendation:

For intervention or exposure studies a structured title should contain information on participants, intervention (exposure), comparison groups, outcomes, and study design (in short known as PICO or IPOC)

Practical points to support implementation of this recommendation:

- Campbell and Cochrane Collaborations suggest to use a specific order of information provided in titles:
  Campbell systematic reviews in education, crime and justice, and social welfare (usually intervention): [intervention/s] for [outcome/s] in [problem/population] in [location/situation]

  Cochrane systematic reviews**:**
  Basic structure: [Intervention] for [health problem]
  Comparing two active interventions: [Intervention A] versus [intervention B] for [health problem]
  Type of people being studied or location of intervention mentioned explicitly: [Intervention] for [health problem] in [participant group/location]
  Not specifying a particular 'health problem' (e.g. 'Home versus hospital birth'), or if the intervention intends to influence a variety of problems (e.g. 'Prophylactic synthetic surfactant in preterm infants'): [Intervention] in OR for [participant group/location].

- Stillwell and colleagues provide a useful template on using the PICOT (patient, intervention, comparison, outcomes, time) format in formulating research questions in other types of research (intervention, aetiology, diagnostic, prognostic or prediction studies, and qualitative studies investigating the meaning of an experience – Fig 1, full report); this template might be useful in guiding researchers in formulating their titles.

Recommendations to improve the quality of titles in IRAS

Currently there are two titles on IRAS. The full title has no word restriction, the short title is limited to 70 characters, no further guidance is given. Options to implement structured titles in IRAS include:

	Option		Advantages / Disadvantages
1	NEW TITLE	Introduce a new title	The advantage would be the freedom to define it as we wish. We wouldn't require adjustment of any past practice However, the disadvantages would be further burden and another title would cause confusion. Applicants would be dissatisfied.
2	USING FULL TITLE	Impose new guidance on the full title	This has adequate length as currently structured. However, it would be difficult to change the full title; it is often a 'given' and it would be difficult to expect changes to this on completing IRAS when it may have been funded and the full title already written.
3	USING SHORT TITLE	Provide new guidance on the short tile and increase the maximum length	This is created when entering data into IRAS. It is thus easier to provide guidance. The disadvantage would be lengthening the short title as our guidance would be difficult with the current 70 character limit. However, brief work suggests 120 characters could accommodate an 'IPOC' (Intervention, Population, Outcome and Comparator) based title and acronym
4	STRUCTURED TITLE IN LAY SUMMARY	Include structured title as first item of lay research summary	This option would not require any structural changes in the form. Possible disadvantage would be limited searching on structured titles as these would be embedded in another field

Proposed actions

- We recommend option 3 changing *Short title* to *Structured title* on IRAS defining a length of 120 characters and writing Question Specific Guidance (QSG) that would explain reasons, purpose, and desired structure along the lines of findings from the review we have conducted.

- We also propose developing this guidance further to support its uptake by wider research and REC communities. The next steps should include:
    - discussion of proposed recommendations with a wider group of different stakeholders (eg researchers engaged in different types of research; members of REC; information specialists; funders; IRAS and HRA professionals and partners, etc)
    - feasibility / pilot study of applying recommendations to improve a sample of deficient study titles submitted for REC review.

Appendix 8

Feedback from patient and public dialogue workshops

All patient groups were supportive of the concept of publishing findings of studies and felt that the HRA could and should do more to encourage publication of findings. One group (Parkinson's group) expressed more caution than the others as they felt that it unless the HRA were able to follow up non-compliance with some leverage that there was no point venturing in to this area and there was a risk of placing an extra layer of bureaucracy:

"Need to be cautious – if you push too hard, you might push them away" (Diabetes Group)

Most patient groups were familiar with online academic journals and portals such as Medline but many of them also expressed concern that most academic publications had restricted access so although researchers might be able to access journals, the general public were generally excluded. One patient said:

"Service users can't access academic journals anyway; they want the information published in a place they can access" (Mental health service users)

All groups suggested that they wanted access to published findings however some groups went on to suggest that they would be happy to see lay summaries. It was suggested that 'lay summaries' could be made available in a different ways, including on the HRA website. Patients also appreciated the importance of 'negative findings' and noted the need not to re-invent the wheel, otherwise *'researchers may run around in circles'* (Diabetes Group). There was a general sense that more could be done to make findings available on the internet and researchers should adhere to *'an open society principle'* (Parkinson's Group). Similar comments included:

"Publishing results in the public arena is a moral obligation" (Cancer patients group)

"There needs to be a culture of open access" (Cancer patients group)

Patients were aware that these changes would not be easy to implement and might require substantial culture change.

In a minority of groups there was an awareness that some studies might be undertaken unnecessarily because previous finding had not been shared. There was concern that without a systematic review, there was an over reliance by both the ethics committee and the funder on the researchers themselves to demonstrate what research had already been undertaken and to justify the need for the study.

Patients were surprised to know that GSK had agreed to publish research findings and felt that more could be done to promote this.

Phase 1 participants expressed an interest in accessing the long term findings for the studies they had been involved in. They were not so much interested in the findings of the study they had participated in, but were keen to know if the study had taken part in had progressed to further stages and if the drug had finally been licensed.

Providing information to participants at the end of the study

Patient groups differentiated between providing general information to participants at the end of study and proving patient specific to individual patients at the end of a study such as informing patients what arm of the study they had been in.

There was a strong feeling in most patient groups that the findings of individual research studies should made available to participants after the study is completed. They recognised that not all participants would welcome knowing the results and so they suggested that participants should be given access to a website where they can access the study findings rather than study findings being sent out *carte blanche*. They acknowledged that there may be good reasons for not feeding back study findings at an individual level, particularly in genetic diagnostic studies where no treatment is available.

There was a suggestion that with some studies with particularly sensitive findings that it might be necessary to provide counselling to participants.

It was also recommended that in the event of the death of a participant shortly after the completion of a study that findings should also be made available to partners or carers.

In terms of providing information to individual participants, there was strong feeling that most participants would want to know what arm of the study they had been in.

Several patients expressed concern that much of the existing focus was the start-up of the study and felt that there was not enough emphasis on what happens at the end of a study.

Role of the HRA in communicating information about clinical trials

Across the board there was an unprompted call for the HRA to communicate with the public about what health research is and clinical trials in particular. They would like to see the work of the research ethic committees given a higher profile in the public arena. The cancer patients group was very clear that the HRA should have a role in raising awareness of clinical trials and also to train general practice in research:

"It is absolutely fundamental that the HRA has a role in raising awareness in research" (Cancer patients)

General public views of the publication of research findings

For many members of the public, research publication was also seen as a key issue. Some argued for the principle of publishing all research believing it to be the ethical duty of researchers to publish their results, and the duty of the HRA or the Research Ethics Committees to ensure that research is published.

Research should all be published: because that would be the right ethical thing to do

London

Could you say that not publishing results is a violation of ethics because the whole process is making sure you protect people? If you have drug Y and it's not published that it failed for some reason and then you test it again and it harms people again

Newcastle

One of the key arguments for publication was that it would improve transparency and accountability in research. The public suggested that asking researchers to publish their results would encourage higher research standards as more people would be able to consider the work that they had done.

'Publication would make them have a better standard. If they published they would have someone to answer to '

London

Members of the public supporting the publication of all research suggested that with more research being published there would be less of a risk of research studies being unnecessarily repeated. This was a particular concern to those participants who were most worried about the risk that research might have on patients.

It would stop duplication down the line

Manchester

If you are only publishing the positive results you are not giving the bigger picture

Manchester

Some members of the public (particularly in London) believed that research publication would significantly improve their trust in medical research and the approval system in a way that other proposals would not.

Acknowledgement

Both the patient and public workshops were part-funded by Sciencewise Expert Resource Centre (Sciencewise-ERC) and were held across England in March and April 2013. The Sciencewise-ERC is funded by the Department for Business, Innovation and Skills (BIS). It aims to improve policy making involving science and technology across Government by increasing the effectiveness with which public dialogue is used, and encouraging its wider use where appropriate to ensure public views are considered as part of the evidence base. [It provides a wide range of information, advice, guidance and support services aimed at policy makers and all the different stakeholders involved in science and technology policy making, including the public. The Sciencewise-ERC also provides co-funding to Government departments and agencies to develop and commission public dialogue activities.] www.sciencewise-erc.org.uk

Useful references

- **Registration**

  Declaration of Helsinki of the World Medical Association (revised 18 October 2008 at Seoul): *"19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject."*

  Research Governance Framework for Health and Social Care Second edition, 2005:

  > In paragraph 3.6.3 one of the responsibilities of the chief investigator is to ensure controlled trials are registered. For other types of research, registration is also encouraged wherever possible. In general, registration is not expected for projects undertaken entirely for educational purposes below doctoral level.

- **Putting results in the public domain**

  Research Governance Framework for Health and Social Care Second edition, 2005:

  > In 2.4.1 the RGF requires free access to information both on research being conducted and on the findings of the research – positive or negative – once these have been subjected to appropriate scientific review.

- **Who will own the data and have rights to publish or disseminate them?**

  ICH GCP indicates that publication policy should be recorded in the protocol (6.15), if not addressed in a separate agreement. Royal College of Physicians guidance:

  > 2.59: It is unacceptable in principle that an investigator should agree to conditions that may prohibit or impair the possibility of publication, though some delay may sometimes be acceptable. This applies whether the sponsor of the research is a pharmaceutical company, a government department or any other agency. Investigators should agree a publication policy in advance and RECs should be aware of what this is.

- **Do sponsors or researchers have possible conflicts of interests that might undermine open access to trial results?**

  IRAS Question A48 Conflicts of interest: Information should be given about any potential conflict of interest for the Chief Investigator or any other investigator or key collaborator in undertaking the proposed research.