



Medicines & Healthcare products
Regulatory Agency



Leadless cardiac pacemaker therapy: design of pre- and post-market clinical studies

Initial recommendations from MHRA Expert Advisory Group

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Contents

1	Introduction	3
1.1.	Remit of the Expert Advisory Group	3
1.2.	Scope of this guidance	3
1.3.	CE marking and dissemination of leadless pacing	3
1.4.	Leadless pacing – background	4
2	Initial recommendations for adoption of leadless cardiac pacing therapy	5
2.1.	Requirements for selection of patients and centres	5
2.2.	Minimum acceptable operator experience and training, to be specified in the manufacturer’s study protocol and/or IFU	5
2.3.	Implant surveillance	6
3	Design of clinical studies for EU market approval and post-market follow-up of leadless cardiac pacing therapy	7
3.1	Introduction	7
3.2	Standard of care (transvenous pacing)	7
3.3	Representative sampling	7
3.4	Sample size and follow-up duration	7
3.5	Grading of adverse events severity	9
3.6	Monitoring of adverse event rates	11
4	Conclusions	11
5	References	11
6	Membership of EAG	11

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1 Introduction

1.1. Remit of the Expert Advisory Group

The leadless devices Expert Advisory Group was commissioned in 2015 by the Device Expert Advisory Committee (DEAC) of the MHRA. It consists of clinical experts (including both those who actively implant such devices and those who do not), together with a clinical and technical representative from MHRA and a further representative from the Association of British Healthcare Industries (ABHI) and the notified body group, TEAM-NB respectively (see [section 6](#) for membership).

The group was convened to provide an expert review of a number of aspects of the clinical evaluation and follow-up of such devices, and first met in December 2015.

The scope of the group was to evaluate requirements for:

- pre-market clinical evaluation of current and planned devices, including advice on pre-market clinical trial design
- post-market clinical evaluation of current and planned devices and evaluation of data gathered in the post-market phase

The group was tasked with producing a framework document aimed at manufacturers and notified bodies to cover best practice in both these areas.

1.2. Scope of this guidance

This guidance applies to new devices and all design changes or iterations and enhancements that might affect the clinical safety or performance of the leadless device. However, each device modification or iteration must be assessed individually to determine whether all aspects of the guidance fully apply (e.g. appropriate follow-up duration for changes that impact only the ease of placement of the leadless device).

While this guidance applies principally to leadless pacing, it is envisaged that it may apply equally to other leadless CIEDs (cardiac implantable electronic devices) as the technology advances. This guidance will be revised periodically as the evidence base for these technologies grows.

1.3. CE marking and dissemination of leadless pacing

CE marking for a medical device indicates a declaration of conformity by the manufacturer (certified by an EU member state's notified body) with the requirements of the EU Medical Devices Directives. This is legally required for the device to be marketed in the EU. CE marking requires demonstration that the device is safe and able to perform as intended but differs from approval of a device by the US Food and Drug Administration as evidence of longer term clinical efficacy is not required at the time of market approval.

MHRA is the UK's competent authority for medical devices and has recognized that leadless pacing is a major departure from conventional cardiac rhythm management (CRM) devices, rather than an iteration of current devices. It is judged to be technology that is not yet well established and for which there are no specific product standards. CE marking has been obtained for leadless pacemakers to date on the basis of limited clinical data, in terms of both the number of patients included in the clinical studies and their follow-up duration.

MHRA wishes to promote innovation in medical technology but would like to see clinical guidance on the use of leadless pacemakers combined with robust surveillance of safety, to ensure that this new technology is used appropriately and that the risk of patient harm is as low as possible. This is clearly in the interests of patients, clinicians and industry as the late identification of safety or training issues could significantly delay the adoption of this potentially important technology.

For this reason, an Expert Advisory Group has been convened, consisting of consultant cardiologists recommended by the British Heart Rhythm Society, some with personal experience of this technology. Input from the medical devices industry has also been sought through the Association of British Healthcare Industries and from the Notified Bodies through TEAM-NB. Based on the recommendations of this group MHRA has issued the following initial guidelines for the adoption of leadless pacing.

1.4. Leadless pacing – background

Implanted pacemaker (PM) therapy for bradycardia has existed for nearly 60 years and has evolved into the implantable cardioverter defibrillator (ICD) for the prevention of sudden death and cardiac resynchronization therapy (CRT) for heart failure. Although the overall efficacy and safety of these CRM devices is excellent, complications can occur, most commonly related to the use of transvenous leads used to connect a subcutaneous implanted generator to the heart. These complications include lead fracture, insulation failure, and infection. Removal and replacement of chronically implanted pacing and especially defibrillation leads can be a major undertaking. Furthermore, transvenous pacing is sometimes difficult or impossible due to occlusion of great veins; and coronary venous anatomy sometimes precludes adequate transvenous cardiac resynchronization.

These considerations have driven the development of leadless pacing systems, of which three have received CE marking (European market approval) at the time of writing. Two (Nanostim[®], St Jude Medical, Inc. and Micra[®], Medtronic, Inc.) are intracardiac, entirely self-contained rate-responsive ventricular demand (VVIR) pacemakers delivered to the right ventricular endocardium via a femoral vein. The third (WICS[®], EBR Systems, Inc.) effectively adds CRT capability to an existing transvenous PM/ICD. It uses a pulse generator or receiver electrode delivered to the left ventricular endocardium via the transfemoral retrograde aortic approach and is powered by an ultrasound transmitter implanted in the chest wall. All three of these devices are delivered through large vascular sheaths and attached to the endocardium by active fixation (a helix or tines).

Other leadless pacing systems are in development and it is thought that this modality may one day provide a wider range of therapies, including multisite endo- or epicardial pacing for CRT plus antitachycardia pacing in combination with non-transvenous ICDs.

2 Initial recommendations for adoption of leadless cardiac pacing therapy

2.1. Requirements for selection of patients and centres

- 2.1.1. Leadless pacing should be considered in patients with a clear indication for bradycardia pacing or cardiac resynchronization.
- 2.1.2. The following should be considered minimum resources for leadless pacemaker implantation:
 - a. cardiac catheter laboratory, with high quality fixed image intensifier with digital acquisition for review and ability to image in all conventional angles
 - b. trained clinical personnel with full resuscitation facilities including defibrillator/external pacing system
 - c. trained clinical personnel with immediate access to echocardiography and equipment for pericardiocentesis
- 2.1.3. Given the very limited intermediate and long-term evidence base for leadless pacing therapy, especially compared to conventional pacing, each patient should have a clear and explicit reason documented for this choice of device over a conventional pacemaker.
- 2.1.4. Careful attention should be paid to contraindications for leadless pacing, such as patient habitus and venous abnormalities likely to result in difficulties/complications from the large sheaths required for device delivery.
- 2.1.5. Patient consent should, in addition to referencing intended benefits of the treatment, explicitly state that early experience with leadless pacing technology has shown a small but significant incidence of serious acute adverse events, including tamponade requiring emergency thoracotomy, device displacement, vascular access issues, etc.
- 2.1.6. In view of the incidence of tamponade and the fact that this has required emergency surgery in a higher proportion of cases than with other invasive procedures, leadless pacemakers should be implanted in centres with on-site cardiac surgery until there are robust data to confirm that the adverse event rate requiring surgery is as low as that associated with conventional pacing (0.1-0.5%).

2.2. Minimum acceptable operator experience and training, to be specified in the manufacturer's study protocol and/or IFU

- 2.2.1. In order to concentrate experience at this early stage, each centre should have a maximum of two operators and both should be encouraged to participate in all procedures. Each should be appropriately trained and proctored, in accordance with the manufacturers' protocols.

- 2.2.2. Operators should be cardiac specialists (consultant cardiologists or cardiac surgeons) with extensive experience of the use of intracardiac catheters and/or leads and the implantation of complex cardiac implantable electronic devices. They should have experience of vascular access using large bore catheters (12F and above) and of manipulation of deflectable catheters in the heart.

2.3. Implant surveillance

- 2.3.1. As well as being recorded in the British Heart Rhythm Society (BHRS) national audit for CRM devices (held by NICOR), all leadless pacemaker implants should be entered into a comprehensive registry or post-market clinical follow-up (PMCF[1]) study, held and funded by the relevant manufacturers and maintained to the standards of good clinical practice. Following CE-marking of the device, implants should not take place outside the registry or PMCF study until at least half the target number of patients has been enrolled and a comprehensive clinical analysis of the safety and performance of the device including one-year patient follow-up has demonstrated a favourable outcome (see section 3 for further details on registry/PMCF study design). The analysis should be undertaken by the manufacturer and reviewed by the notified body with independent clinical input as appropriate to these organisations. It should be made available to MHRA on request.
- 2.3.2. The PMCF study or registry should include, but not be limited to, collection of information on:
- a. relevant patient demographics
 - b. indication(s) for pacemaker/CRT therapy
 - c. rationale for the choice of leadless approach
 - d. acute implant outcomes
 - e. implant location within heart (apex, mid-septum etc)
 - f. in-hospital, 30-day and 1-year device performance, adverse events and all-cause mortality
 - g. MR scans (static field strength and body site scanned) and any adverse events arising affecting the device or patient.
 - h. interaction with/from other implanted or external devices
 - i. device explant or deactivation
 - j. long-term device/battery performance and late complications
- 2.3.3. Information held in the PMCF study or registry should be reported publically at pre-specified intervals (either of time or recruitment numbers) and made available at all times on request to MHRA.
- 2.3.4. The manufacturer's broader post-market surveillance strategy should ensure that information on the safety and performance of the leadless device is collected for the lifetime of the implant. This will enable an assessment to be made of the risks associated with either explanting the device or leaving it in situ, when it reaches end of life. It is important that information is captured on any mechanical or electrical interactions between an abandoned leadless device and the replacement pacing system.
- 2.3.5. Adverse incidents should be assessed for reportability to regulatory authorities according to the requirements set out in the applicable MEDDEV reporting guidelines [1].

3 Design of clinical studies for EU market approval and post-market follow-up of leadless cardiac pacing therapy

3.1 Introduction

It is important that studies are designed to answer specific questions about the safety and efficacy of new devices which cannot be answered through bench or animal testing. The results of clinical studies should be compared with a suitable 'standard of care' treatment where possible.

Studies to obtain market approval (CE-marking) for novel treatments are likely to be relatively small in size, to avoid excessive delay in patient access to promising new treatments, so it is essential to minimise bias and to make the inherent design limitations explicit. For the statistical assumptions used in data analysis to be appropriate, it is essential that the study design is agreed in advance with regulators and not altered without reassessment of the statistical design. Such studies can, at best, explore adverse event rates associated with short or medium-term implant durations. Therefore, they should, except in exceptional circumstances, be supplemented by PMCF studies or registries to evaluate the longer-term safety and performance of the new or novel treatment. PMCF study and registry requirements should also be based on learnings during pre-market evaluation.

3.2 Standard of care (transvenous pacing)

The current standard treatment for the condition should be described in detail including published evidence of efficacy, safety (short-, medium- and long-term adverse event rates) and (where available) cost-effectiveness. This can then be used to judge the relative merits of the new treatment.

3.3 Representative sampling

It is essential that patients taking part in the study are representative of the patients who will be treated in clinical practice. The clinical indications for which the device achieves market approval must be based on evidence gained from equivalent patients included within the pre-market study. Approved patient indications should be clearly defined and specified in device labelling at the time of approval. Any extension to approved patient indications should be investigated within a new pre-market clinical investigation.

1. Inclusion criteria must be clear and representative of the population to be treated
2. Exclusion criteria must be clear and representative of groups of patients for which the treatment is not appropriate

3.4 Sample size and follow-up duration

The sample size required will depend on:

1. The nature and seriousness of the anticipated adverse events. For some adverse events, only those occurring in 5% of patients may be important. For other adverse events (mortality for example), a 1% (or less) rate may be unacceptable. Patient numbers should

enable an adequately powered comparison with established adverse event rates associated with clinical alternatives. Adverse event rates against which to compare study results must be pre-specified, and selected from accepted data on 'standard of care treatment' established in published literature.

2. The type of study - pre-market (gathering data for approval) or post-market. For pre-market studies, wider confidence intervals and lower power may be acceptable in order to achieve a compromise between adequate assessment of short and medium-term device safety and the avoidance of undue delay in patient access to the novel treatment. For PMCF studies or registries, greater confidence in the accuracy of the study results is essential, leading to the need to select a sample size achieving results with narrower confidence intervals and greater power.
3. Specific performance criteria

Table 1 provides guidance on suitable z values (upper-bound confidence intervals) for different adverse event rates under investigation, with corresponding sample sizes for pre- and post-market studies. The sample size chosen for any study must be calculated based on the specific study hypothesis and documented in advance in the trial design.

The patient follow-up duration will also depend on the study objectives and endpoints, the anticipated profile of adverse events and whether the study is conducted for device approval or post-market evaluation. For any permanent implant, long-term clinical data are essential to demonstrate the true safety and efficacy of the treatment option. However, for pragmatic reasons the scope of a pre-market study is typically restricted to the assessment of stated performance claims and short/medium term adverse events. In all cases a robust, study specific, justification should be provided for approval studies which are designed to gather clinical experience for less than one full year of patient follow-up.

Table 1 – Recommended minimum sample sizes and follow-up durations

Adverse event rate under test (% patients)	CE-approval study				Post-approval studies/registries			
	Sample size to give 80% power to have a 95% CI with an upper bound below z%				Sample size to give 90% power to have a 95% CI with an upper bound below z%			
	Upper bound CI (z%)	Appropriate sample size range (patient number)	Maximum permitted events if min sample size used	Min patient follow-up duration (months)	Upper bound CI (z%)	Appropriate sample size (patients number)	Maximum permitted events if min sample size used	Min patient follow-up duration
1	4.7	150-250	2	12	2.5	> 900	13	PMCF study: 3 years Registry: 5 years
2	7.7	130-200	4		4.2	> 700	19	
3	9.9	100-150	4		5.7	> 600	23	
4	12.5	90-120	5		7.5	> 500	26	
5	14.7	80-110	6		9.4	> 400	26	
6	16.6	70-100	6		10.7	> 300	27	

Confidence intervals to be based on exact binomial distribution

+Number of events linked to the minimum sample size such that upper bound CI < z%

Consideration should also be given to the use of Kaplan-Meier (or other methods that allow for patient censoring for reasons unrelated to endpoint outcome) to estimate adverse event rates in longer-duration post-market studies due to the relatively older age and high prevalence of co-morbid conditions for many patients requiring pacing therapies.

3.5 Grading of adverse events severity

The severity of adverse events should be graded in a similar way to other internationally accepted scales as listed below.

Grade 1

Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2

Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental, ADL (activities of daily living).

Grade3

Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

Grade 4

Life-threatening consequences; urgent intervention indicated.

Grade 5

Death related to adverse event.

Table 2 gives examples of the types and grade of severity of adverse events.

The adverse events should also be categorised in terms of their relationship to the device or the procedure, in accordance with ISO 14155:2011 [2].

Table 2 Examples of adverse events related to pacemaker implantation

	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe or medically significant)	Grade 4 (life-threatening)	Grade 5 (death)
New pericardial effusion	Small asymptomatic e.g. <10mm effusion on echo	Asymptomatic e.g. 10-20mm effusion on echo	Effusion with physiological consequences	Tamponade; requiring drainage or surgical intervention	Death
Pneumothorax	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; intervention indicated (e.g., tube placement without sclerosis)	Sclerosis and/or operative intervention indicated; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Vascular damage	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL	Life-threatening consequences; urgent/surgical/thrombin injection intervention indicated	Death
Haematoma	Mild symptoms; intervention not indicated	Minimally invasive evacuation or aspiration indicated, delayed hospital discharge	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent surgical intervention indicated	Death

3.6 Monitoring of adverse event rates

Each adverse event should be reviewed by an independent data monitoring committee [2]. The circumstances leading to each adverse event should be analysed with a view to reducing the likelihood of a recurrence.

Interim safety analyses should be performed based upon pre-specified criteria. For example, if there are ≥ 3 serious (grade 4-5) adverse events in the first 59 patients, this indicates that there is 95% confidence that the adverse event rate is $\geq 1\%$ and may suggest a re-evaluation of the proposed treatment or its performance.

If a higher than expected adverse event rate is observed, it may be appropriate to discontinue the study unless/until the causes have been identified. Significant changes to the device, implant technique, or patient selection process may be needed to reduce the risks. A new study or a study modification should then be proposed incorporating the safety data from the initial study. For study modifications the data collection should be sufficiently segregated to enable both separate and combined analysis with respect to the original study data, to ensure the impact of any changes can be measured.

4 Conclusions

Each new treatment will have a unique pattern of risks and benefits and have a different standard of care as its comparator. Nevertheless, this document provides advice on general statistical principles which can guide decision making in the study conduct and design.

5 References

- 1 European Commission, [MEDDEV 2.12/2 rev 2 Post Market Clinical Follow-up Studies](#)
- 2 ISO 14155:2011 Clinical investigation of medical devices for human subjects – good clinical practice.

6 Membership of EAG

Prof Nicholas Linker, James Cook University Hospital, Middlesbrough (President BHRS), Chair

Dr Francis Murgatroyd, King's College Hospital, London (Audit Lead, BHRS)

Dr Chris Plummer, Freeman Hospital (proposed by BHRS and CRM device clinical specialist advisor to NICE)

Dr Paul Roberts, Southampton General Hospital (leadless pacing implanter)

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