National Patient Safety Agency

National Research Ethics Service

Approval for medical devices research

Guidance for researchers, manufacturers, research ethics committees and NHS R&D offices

Version 2 March 2008

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Introduction and summary

1. These guidance notes are intended to assist researchers, medical device manufacturers, members of research ethics committees (RECs) and NHS[1] R&D offices in understanding arrangements for regulation and ethical review of trials of medical devices in the UK, and to give practical guidance to applicants.

2. The guidance has been developed in collaboration between the following bodies:

   - Medicines and Healthcare products Regulatory Agency - Devices Division (MHRA)
   - National Research Ethics Service (NRES)
   - Association of the British Healthcare Industries (ABHI)
   - Institute of Clinical Research (ICR)
   - NHS R&D Forum.

3. The guidance highlights differences between *clinical investigations* of non-CE marked medical devices and *post-market studies* on CE Marked devices being used for their intended purpose. It also emphasises the differences between the regulatory requirements for clinical investigations of *medical devices and pharmaceuticals*, and the impact of this on the design of clinical investigations.

4. The guidance is divided into the following sections (click on section heading for a quick link)

5. For specific advice on issues in particular trials please refer to the list of contacts in section 11.

[1] In this document, references to the NHS include the Health and Social Care (HSC) system in Northern Ireland.

6. If you have any comments on this guidance please contact queries@nres.npsa.nhs.uk.

Summary of key points

7. All medical devices placed on the UK market have to comply with device-specific legislation. This results from the UK having transposed into its national laws a series of European medical device Directives framed in the 1990s. The regulatory system in the UK is governed by the Medical Devices Regulations 2002. The designated Competent Authority for medical devices in the UK is MHRA (Devices Division); this is the successor body to the previous Medical Devices Agency.

8. The Medical Devices Directives contain a wide-ranging and comprehensive list of Essential Requirements. The device manufacturer is obliged to ensure that his device meets each relevant Essential Requirement and to demonstrate that this is so by completing the relevant conformity assessment procedures.

9. Where conformity assessment demonstrates that no new clinical data is necessary to CE mark the new device, the manufacturer may need to carry out clinical studies as part of post marketing surveillance requirements or to generate other data, such as user preferences. In these cases no application to MHRA is necessary, but application to a REC may be required. Where the clinical study is conducted in the NHS, NHS permission for research will also be required.

10. Where the manufacturer has determined that additional data from a ***clinical investigation*** is necessary for conformity assessment, the manufacturer must inform MHRA Devices and provide details of the investigational device and the proposed study. MHRA Devices has 60 days in which to make an assessment of the information supplied. Authorisation is given in the form of a Notification of No Objection.

11. As part of the final authorisation, MHRA will require a copy of a favourable opinion from a relevant REC. Where the clinical study is conducted in the NHS, NHS permission for research will also be required. The ethical opinion and NHS permission can be obtained in parallel with the Competent Authority Notification.

12. Applications to MHRA, the REC and relevant NHS R&D offices can all be made using the Integrated Research Application System (IRAS).

13. NRES has designated a panel of RECs ("flagged RECs") to review applications involving medical device research.

14. The ethical issues in medical devices research are broadly the same as for any other research. However, there are important differences in the regulatory context, research environment and methodology, and particularly in the area of investigation design. Members of flagged RECs attend training at which these differences are explored.

15. The end points for clinical investigations are safety and performance (as claimed by the manufacturer) and do not require demonstration of efficacy. This means that the design of devices investigations is often different from pharmaceutical studies with randomised controlled trials seldom being employed. This will also have a direct effect on the statistical methodology employed.

16. There are distinct procedures for notifying protocol amendments and submitting safety reports to the MHRA, RECs and NHS R&D offices.

17. Separate guidance is available on communications between MHRA and RECs on medical device studies.

1. Background to the UK regulations

1.1 The Medical Devices Regulations 2002 (Statutory Instrument 2002/618) came into force on 13 June 2002 and implement the provisions of the:

- Medical Devices Directive 93/42/EEC
- Active Implantable Medical Devices Directive 90/385/EEC
- In Vitro Diagnostic Medical Devices Directive 98/79/EEC.

These Regulations establish systems under which a manufacturer must submit to the UK Competent Authority, information about clinical investigations of medical devices to be carried out in the UK.

1.2 *Medical Devices Directive*. This covers most general medical devices over a wide range of products from simple bandages to orthopaedic implants and high technology radiology equipment. Regulations implementing the Directive came fully into force in the United Kingdom on 13 June 1998.

1.3 *Active Implantable Medical Devices Directive*. This covers all powered medical devices implanted and left in the human body, such as pacemakers, implantable defibrillators, implantable infusion pumps, cochlear implants and implantable neuromuscular stimulators. The Directive also covers implanted passive parts of active devices such as pacemaker leads and adapters, and external parts that are an essential part of the systems, e.g. pacemaker programmers. Regulations implementing the Directive came fully into force in the United Kingdom on 1 January 1995.

1.4 *In Vitro Diagnostic Medical Devices Directive*. This Directive covers any medical device, reagent, reagent product, kit, instrument, apparatus or system which is intended to be used for the in-vitro examination of substances derived from the human body, such as blood grouping reagents, pregnancy testing and Hepatitis B test kits. Regulations implementing the Directive came into force in the UK on 7 June 2000 with a transitional period until 7 December 2003. There is no clinical investigation system for in-vitro diagnostic medical devices. Performance evaluations of in vitro diagnostic devices that are performed outside the manufacturer's premises in the UK should be notified to the UK Competent Authority in accordance with the Medical Devices Regulations 2002: Section 44.

1.5 The main purpose of these Directives is to allow free movement of medical devices throughout the European Community, whilst at the same time ensuring device performance and safety. The Directives replace any existing national systems in each Member State.

1.6 In summary, these three Directives:

- specify the medical devices to which they apply;
- specify the Essential Requirements which must be met before any device can be placed on the market or put into service and which are intended to ensure that:

    - a device does not compromise the clinical condition or safety of the patient, the safety and health of users or, where applicable, any third party;
    - a device achieves its intended purpose as designated by the manufacturer; and
    - any risks associated with the use of the device are acceptable when weighed against the benefits to the patient and compatible with a high level of protection of health and safety.

- introduce controls covering the safety, performance, specification, design, manufacture, labelling and packaging of devices;

- specify the requirements for pre-clinical assessment of clinical investigation notifications;

- introduce the concept of risk classification (the higher the risk associated with the device, the greater the level of independent assessment required before the product can be placed on the market);

- specify the action to be taken, if any, following a device-related adverse incident;

- require Competent Authorities to check that manufacturers have met the relevant requirements by carrying out activities such as auditing of quality systems, testing of devices and review of technical documentation.

1.7 These controls are intended to ensure the safety and performance of medical devices and to prohibit the marketing of devices which might compromise the health and safety of patients, users or any relevant third party (where appropriate).

1.8 Manufacturers wishing to make an application for pre-clinical assessment of a proposed clinical investigation of an active implantable medical device or a general medical device to be carried out in part or in whole in the UK should apply to MHRA, an Agency of the Department of Health (referred to in this document as the UK Competent Authority). Further information about applying to the MHRA is in section 6 of this guidance.

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2. Requirements of the UK regulations

CE Marking

2.1 In order to be able to CE mark any device, a manufacturer must demonstrate that the stated device complies with the relevant Essential Requirements. To demonstrate such compliance, it will usually be necessary to provide clinical data, which may be in one of two forms:

- either a compilation of the relevant scientific literature currently available on the intended purpose of the device and the techniques employed, together with, if appropriate, a written report containing a critical evaluation of the compilation (the literature/clinical evaluation route); or

- the results and conclusions of a specifically designed clinical investigation (the clinical investigation route).

The literature/clinical evaluation route

2.2 Critical analysis and evaluation of scientific literature are broad concepts which can take account of the experience of the device in question or of an established device or class of device which is already on the market and used in clinical practice and with which equivalence can be demonstrated in terms of technology, critical performance, design, principles of operation, population involved, conditions of use and clinical purpose.

2.3 Where the manufacturer's clinical evaluation of the scientific literature concludes that there is adequate data to demonstrate that the stated device complies with the relevant Essential Requirements, no clinical investigation needs to be carried out prior to CE marking.

The clinical investigation route

2.4 However, unless safety and performance can be adequately demonstrated by other means, data generated from a specifically designed clinical investigation of a medical device is likely to be required. Such an investigation must be designed:

- to verify that under normal conditions of use the performance characteristics of the device are those intended by the manufacturer; and

- to determine any undesirable side effects under normal conditions of use and to allow an informed clinical opinion to assess whether these are acceptable when weighed against the benefits in relation to the intended performance of the device.

2.5 Thus a clinical investigation of a non-CE-marked device must be designed to establish that the performance claimed by the manufacturer can be adequately demonstrated, and that the device is judged to be safe to use on a patient taking into account any risks associated with the use of the device when weighed against the expected benefits. If the purpose of a proposed clinical investigation is other than as outlined above, e.g. user handling or

preference studies, it should not be carried out on a non-CE-marked device. Such studies should only be performed on CE-marked devices unless they form part of a study to investigate safety and performance.

2.6 Likewise, any clinical investigation of a medical device that requires the use of specially designed accessories (e.g. surgical tools or delivery systems) must also be designed to investigate the safety and performance of these accessories if they are not CE-marked for the purpose being investigated.

2.7 Before devices intended for clinical investigation in the UK are made available to a medical practitioner for the purposes of clinical investigation, the manufacturer of the device (or his authorised representatives in the European Union) must give 60 days prior notice to the Secretary of State for Health by writing to the UK Competent Authority.

2.8 If, within 60 days of formal acceptance of the Notice, the UK Competent Authority has not given written notice of objection, the clinical investigation may proceed. The UK Competent Authority may give such notice of objection on grounds relating to public health or public policy (Medical Devices Regulations 2002 section 16(4), section 29(3)). *In practice, the MHRA always issues a letter within 60 days either to give notice of objection or to confirm that there is no objection.*

2.9 The legal requirements as to methodology and ethical considerations relating to clinical investigations are set out in the Medical Devices Regulations 2002: section 16 and section 29, the Active Implantable Medical Devices Directive, Annexes 6 and 7, and the Medical Devices Directive, Annexes VIII and X. In particular the clinical investigation must:

- be performed on a basis of an appropriate plan with well-defined aims and objectives;
- make use of procedures appropriate to the device under examination;
- be performed in circumstances similar to the intended conditions of use;
- include sufficient devices to reflect the aims of the investigation taking into account the potential risk of the device;
- examine appropriate features involving safety and performance and their effects on patients so that the risk/benefit balance can be satisfactorily addressed;
- fully record all adverse events and report serious adverse events to the UK Competent Authority;
- be performed under the responsibility of a medical practitioner or a number of medical practitioners; and
- include the making of a final written report, signed by the medical investigator(s) responsible, which must contain a critical evaluation of all the data collected during the clinical investigation, with appropriate conclusions.

2.10 Additionally, the principles of clinical investigations of medical devices are set out in the Standard BS EN ISO 14155-1; 2002, *"Clinical Investigation of Medical Devices for Human Subjects-part 1: General Requirements"*, and BS EN ISO 14155-2:2002, *"Clinical Investigation of Medical Devices for Human Subjects- part 2: Clinical Investigation Plans".* These are harmonised Standards providing presumption of conformity with Annex 7 of the Active Implantable Medical Devices Directive and Annex X of the general Medical Devices Directive.

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3. Clinical investigations and post-market studies

Is a clinical investigation required?

3.1 A clinical investigation of a non-CE-marked medical device should at least be considered in the following circumstances:

- the introduction of a completely new concept of device into clinical practice where components, features and/or methods of action, are previously unknown;
- where an existing device is modified in such a way that it contains a novel feature particularly if such a feature has an important physiological effect; or where the modification might significantly affect the clinical performance and/or safety of the device;
- where a device incorporates materials previously untested in humans, coming into contact with the human body or where existing materials are applied to a new location in the human body, in which case compatibility and biological safety will need to be considered;
- where a device, either CE-marked or non-CE-marked, is proposed for a new purpose or function;
- where *in vitro* and/or animal testing of the device cannot mimic the clinical situation;
- where there is a new manufacturer especially of a high-risk device.

3.2 Where the manufacturer's clinical evaluation of the scientific literature concludes that there is ***inadequate data*** to demonstrate that the stated device complies with the relevant Essential Requirements, a clinical investigation will need to be carried out. Clinical investigations require regulatory approval by MHRA, ethics approval from a REC and NHS permission for research from relevant healthcare organisations.

3.3 Where the manufacturer's clinical evaluation of the scientific literature concludes that there is ***adequate data*** to demonstrate that the stated device complies with the relevant Essential Requirements, no clinical investigation needs to be carried out prior to CE marking.

Clinical investigations: special circumstances

Change in the intended use of a device

3.4 Clinical data may be required in the case of a device already authorised to carry the CE marking, where that device is to be used for a new purpose and eventually CE marked for that new purpose. These clinical data may need to be generated by a specifically designed clinical investigation, in which case a notification must be made to the UK Competent Authority.

Devices manufactured in-house in a healthcare establishment

3.5 Devices manufactured in-house in a healthcare establishment are usually produced as a one-off model or in small numbers to determine proof of concept. Provided such devices are used within the same legal entity and on the patient(s) of that Trust, then the device(s) are not subject to the provisions of the Medical Devices Regulations.

3.6 If, however, the device is sold or given to another legal entity, or in circumstances where the in-house manufacturer sees and intends a commercial application in the results generated (irrespective of whether the manufacturer and subjects are part of the same legal entity) then the provisions of the Medical Devices Regulations apply. In these circumstances, where a clinical investigation is proposed, application must be made to the UK Competent Authority.

3.7 It should be noted that the in-house manufacturer may sub-contract the manufacture of parts of the device to a commercial manufacturer without affecting these requirements.

3.8 If there is any doubt in interpreting these requirements, the Competent Authority should be contacted for clarification.

Off-label use

3.9 If a clinician uses a CE marked device for a new or off-label purpose, which is unsupported by the manufacturer, then the clinician in the relevant healthcare establishment may take on liability in the event of an adverse incident. Such use must therefore be authorized by the healthcare establishment through its own local procedures, even if the activity is not as part of a research project.

3.10 The clinician and the relevant healthcare establishment may also take on the responsibilities of the "manufacturer" if they see or intend a commercial application and must, therefore, fulfil the requirements for the manufacturer as set out in the Medical Devices Regulations 2002, including notification to the UK Competent Authority.

3.11 The manufacturer may not sponsor a clinician to evaluate a new or off-label purpose for a device outside of a formal clinical investigation.

Post market studies

3.12 Where a clinical investigation is not required, manufacturers may nevertheless choose or be obliged to carry out clinical or observational studies in the post-market phase on the CE Marked device. These post market studies do not require review or approval by the UK Competent Authority but may need ethics approval from a REC (see paragraphs 5.2–5.5).

3.12 Manufacturers may elect to carry out user preference studies, patient outcome studies, reimbursement studies etc using a variety of trial designs.

3.13 In order to meet the regulatory requirements for post-market surveillance, manufacturers may carry out observational studies to monitor the long-term performance of their devices. This will be particularly the case with

implantable and other high risk devices, e.g. a hip replacement.

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4. Functions of the UK Competent Authority

4.1 The UK Competent Authority has 60 days in which to make an assessment of the submitted documentation on a clinical investigation and may raise grounds for objection based on issues of public health.

4.2 The Competent Authority will make an assessment of the documentation which will include the following where relevant:

- protocol
- device detail and design
- materials
- toxicology and biological safety
- sterilization validation
- electrical safety
- safety and usefulness of medicinal substance
- safety and appropriateness of use of tissues of animal origin

4.3 If, after consideration of all the evidence provided, the Competent Authority considers that there are no grounds relating to health or safety or public policy whereby the proposed clinical investigation should not proceed, the Competent Authority will notify the applicant of this decision and provide them with a Notification of No Objection letter.

4.4 If, after consideration of all the evidence provided, the Competent Authority considers that the proposed clinical investigation may present unjustifiable risks to public health or safety, the Competent Authority will notify the applicant of its objection to the commencement of the proposed clinical investigation.

4.5 The reason for raising grounds for objection will be fully set out in the final letter. Manufacturers may resubmit their application provided these grounds have been addressed.

4.6 However, the Competent Authority has the right to withdraw a written Notice of No Objection if, in its opinion, serious adverse events that occurred during the course of the trial give rise to issues of public health.

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5. Requirements for ethical review and NHS permission

Requirements for ethical review

5.1 Ethical review should always be sought for a clinical investigation of a non-CE marked medical device, a performance evaluation of an in vitro diagnostic device, or other research involving a medical device.

5.2 It is not required for most “non-interventional” post-market surveillance studies of a CE Marked product, which are considered to be service evaluations.

5.3 A "non-interventional" study of a CE marked product is defined in this guidance as one that meets all of the following criteria:

- The product is used within its intended purpose
- The assignment of any patient involved in the study to a particular therapeutic strategy or diagnostic procedure is not decided in advance by a protocol but falls within current clinical practice
- The decision to use the product is clearly separated from the decision to include the patient in the study
- No diagnostic or monitoring procedures are applied to the patients included in the study, other than those which are ordinarily applied in the course of current clinical practice
- Epidemiological methods are to be used for the analysis of the data arising from the study.

5.4 An example of a non-interventional study using epidemiological methods would be a follow-up of a make of hip prosthesis. Provided follow-up occurred only at times when surgical practice would require it, and was limited to investigations that would be done anyway, the study would be non-interventional. The epidemiological methods would be the analysis of the prosthesis failure rate, calculated using life table methods, a standard epidemiological tool.

5.5 However, a post-market surveillance study should be submitted for ethical review if it does ***not*** meet the criteria for non-interventional studies of CE marked products. In particular the following should always be treated as interventional studies and ethically reviewed:

- Randomised controlled trials;

- Case series studies involving *additional research procedures*, e.g. additional blood samples or radiography, or investigations outside those that would normally be employed in the routine management of the patient.

5.6 It should be noted that all post-market surveillance studies require a protocol and an informed consent form to obtain consent for access to medical notes and processing of identifiable patient data.

5.7 For further information and examples on whether ethical approval is required, please refer to the flowcharts in Annex A – Taxonomy of Medical Device Clinical Studies and Annex B – Decision Tree (both reproduced with permission of the author Mick Borroff of the ABHI).

5.8 Additional guidance on differentiating audit, service evaluation or research can be found at: http://www.nres.npsa.nhs.uk/rec-community/guidance/#Researchoraudit

5.9 The Governance Arrangements for NHS Research Ethics Committees (GAfREC) set out the remit of NHS RECs. Further advice is available from: http://www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4005727&chk=CNcpyR

5.10 If you are still unsure whether you require ethical review you may seek advice from the R&D office at the lead site for the project, from the Chair of a flagged REC (see contact details at http://www.nres.npsa.nhs.uk/contacts) or from the NRES Queries Line by writing to queries@nres.npsa.nhs.uk.

5.11 It is recognised that some journals may seek evidence that ethical review is not required before agreeing to publish the results of post-market surveillance, even where it is non-interventional. Foreign regulators such as the US Food & Drug Administration (FDA) may also require confirmation that ethical review is not required where a study is being used to generate data for regulatory approval outside the UK. If so, please request confirmation in writing from a REC flagged for review of the medical devices research or from queries@nres.npsa.nhs.uk.

5.12 If the journal or regulatory authority requires full ethical review, an application may be submitted. When completing the Project Filter in the Integrated Research Application System, please select the category *"Research study on a CE Marked medical device"*. It would be helpful to explain in a covering letter to the REC why, exceptionally, an application is being made.

NHS permission for research

5.13 Under the Research Governance Framework for Health and Social Care, research undertaken in or through the NHS requires management permission from each NHS organisation concerned. This applies to all research involving NHS patients or their tissue/data, research involving NHS facilities, and research carried out by NHS staff as part of their employment. Permission for research should be sought from the relevant R&D office ("R&D approval").

5.14 *Interventional* post-market surveillance studies (see paragraph 5.5-5.6) are categorised as research and require NHS permission for research, if the research is being conducted within the NHS.

5.15 Projects classified as audit or service evaluation are not managed as research within the NHS and do not require management permission. *Non-interventional* post-market surveillance studies, therefore, do not require permission. However, manufacturers should check with the Clinical Governance Office at the NHS care organisation what other review or oversight arrangements apply to audit and service evaluation projects. It should be noted that all post-market surveillance studies require a protocol

and an informed consent form to access medical notes or process identifiable patient data outside the clinical care team. Advice on this may be sought from the Caldicott Guardian at the NHS care organisation.

5.16 The NHS R&D Forum publishes guidance on NHS research governance arrangements at http://www.rdforum.nhs.uk.

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6. How to apply for approvals and permissions

Integrated Research Application System (IRAS)

6.1 The Integrated Research Application System (IRAS) is a common system for applying for a range of approvals and permissions for research in the UK. It is designed to facilitate the approval process by allowing researchers to enter common information in the same system, without duplication. All relevant guidance is available in IRAS or by links to other web pages.

6.2 For medical devices research, IRAS can be used to apply to:

- MHRA (Devices Division)
- Research ethics committees
- NHS R&D offices

6.3 To use IRAS, go to https://www.myresearchproject.org.uk/. Follow the instructions to create a user account, or enter your existing login and password if you already have an account. A guidance manual for users is available on the Help page at: https://www.myresearchproject.org.uk/Help/Information.aspx.

6.4 For guidance on completing application forms in IRAS, please see the question-specific guidance linked to each question or available in collated form on the "Help" page (see link above). If the guidance does not answer your query, please contact the relevant review body using the contact points listed in IRAS under "Contact Us". For technical queries on using IRAS, please contact the IT Helpdesk at helpdesk@infonetica.net.

6.5 When you create a new project in IRAS, you will be asked to complete the Project Filter. This is the key to generating the relevant application forms and questions, which are customised according to the type of study and the review bodies to which you need to apply. Guidance is available next to each question in the Project Filter.

6.6 Once you have completed the Project Filter, you will be able to view the full dataset for your Project on the Navigate page, as well as the individual application form(s) for different bodies. To complete your forms, you may either open the full dataset or start with a particular form. Common data is automatically populated to other forms where required.

6.7 For advice on submission arrangements for each review body, highlight the appropriate form on the Navigate page and select the "Submit" option on the right hand side. Applications may be submitted in parallel or in sequence (in any order).

Combined drug/device investigations

6.9 If you are conducting research on a drug/device combination product, you are strongly recommended to obtain expert advice on the regulatory requirements before you complete the IRAS Project Filter and proceed with your applications. You may seek advice from either branch of the MHRA as follows:

- MHRA (Medicines) – contact the Clinical Trials Helpline for medicinal trials at clintrialhelpline@mhra.gsi.gov.uk or 0207 084 2327

- MHRA (Devices Division)– use the contact points at the foot of the following page: http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=194

Flagged RECs

6.10 NRES operates a system of "flagging" of RECs for ethical review of certain types of application. Medical devices research is one of the application types for which RECs may be flagged.

6.11 Although not mandatory, it is strongly recommended that applicants for medical devices research apply to a flagged REC. This should be arranged by booking the application through the NRES Central Allocation System (CAS) – telephone number 0845 270 4400 (weekdays from 9.30 a.m. to 4.30 p.m.).

6.12 RECs are selected for flagging primarily because they have an interest in a particular area of research and relevant experience from previous applications. Members of flagged RECs will have attended relevant training. Flagged RECs may also have members with relevant professional or scientific expertise, though they are not specialist scientific committees. They continue to receive a wide range of applications other than in the area of special interest, and apply the same generic principles to all ethical review. The advantage of applying to a flagged REC for medical devices lies mainly in their familiarity with and understanding of the regulatory context and typical approaches to study design and methodology in the devices setting.

6.13 The flagged RECs for medical devices are listed on the NRES website. Changes to the list of flagged RECs may be made from time to time.

6.14 For further guidance about applying for ethical review, see: http://www.nres.npsa.nhs.uk/applicants/apply/applying-for-ethical-review/

Site-specific assessment (SSA)

6.15 For all clinical research, Site-Specific Assessment (SSA) is always required as part of the ethical opinion. The Principal Investigator at each site in the research should apply for SSA by completing the Site-Specific Information (SSI) Form in IRAS. The application for SSA can be made once the main application form for ethical review has been submitted to the main REC and accepted as valid for review. Detailed guidance on submission arrangements is available in IRAS.

6.16 For NHS sites throughout the UK, the SSA will either be carried out by the REC or by the local NHS R&D office, depending on local arrangements. Responsibility for SSA is gradually being transferred from RECs to R&D offices. Before submitting, applicants are advised to check the position locally.

6.17 For research sites outside the NHS, the SSA will be carried out by an appropriate local REC. If you are unsure which REC to apply to, please seek

advice from the RES operational manager for the area, using the contact details on the website.

6.18 The outcome of the SSA will be notified to the main REC by the local assessor (whether a local REC or R&D office) within 25 days of the application being submitted. If there is no objection from the assessor, the main REC will then confirm ethical approval for the site in writing to the Chief Investigator.

6.19 SSA is generally not required for non-clinical research, including:

- Research limited to use of tissue or data (including performance evaluations of IVDDs)
- Research limited to use of questionnaires
- Research involving qualitative methods (e.g. quality of life assessments)
- Post market surveillance studies (where exceptionally ethical review is indicated).

6.20 The main REC will confirm whether or not SSA is required when validating the main application.

Publication of lay summary and ethical opinion

6.21 The REC application form includes a lay summary. This should be a short summary of the proposed research, written in a form suitable for disclosure under the Freedom of Information Acts (FOI). The summary should describe in lay language the background to the research, the questions it will answer and potential benefits, the study design and what is involved for participants.

6.22 Where exemptions could apply under the FOI Acts to particular information in the application (e.g. likely prejudice to commercial interests, risk to health and safety of any person, personal data), applicants are advised to exclude such information from the lay summary.

6.23 NRES plans to publish lay summaries of all REC applications, together with a summary of the ethical opinion. The purpose of this is to inform the public and patients about current research and the work of RECs, and to comply with requirements under FOI to publish information held by public bodies.

6.24 Lay summaries will be published for all applications submitted from 1 May 2008. It is planned to introduce publication of the summary ethical opinion later in 2008.

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7. Ethical Review

7.1 This section provides guidance both for REC member and applicants. It is important that there is a mutual understanding of the principles underpinning ethical review of research.

7.2 Regulatory issues for medical devices are different to those for pharmaceuticals. Clinical investigations aim to demonstrate safety and performance as claimed by the manufacturer, not efficacy, so there will usually be differences in study design. Randomised trials are rarely indicated or feasible.

7.3 However, the moral principles that underpin fair research are the same, regardless of whether the object of the study is a service, a medicine or a medical device. Consequently research in these domains can be analysed using similar ethical models.

7.4 Whatever the nature of the project the applicant and REC members need to consider:

> "The PURPOSE of the study is ……. The NEED is …… The DESIGN is …….. Subjects will be RECRUITED in such and such a manner. CONSENT will be obtained in …….. way. CONFIDENTIALITY has been protected by……. If something goes wrong REDRESS will be available….."

PURPOSE	Is a purpose defined and will it be achieved?
NEED	Is the study worthwhile?
DESIGN	What are the risks, burdens and benefits to the subject?
RECRUITMENT	Will subjects be recruited fairly?
CONSENT	Will there be fair assessment of the subject's capacity to consent for themselves?
	Will adequate information be given upon which subjects can decide?
	Is it clear there will be no coercion?
CONFIDENTIALITY	Will information about subjects be appropriately handled?
REDRESS	Would there be fair redress if a subject were harmed in any way?

The environment of devices trials

7.5 Nevertheless the environment of devices research is different to that of the "medicines" world. There are considerable regulatory differences that a REC

must understand and work within. Issues with regulation are for MHRA Devices, and are explained earlier in this guidance (see sections 1-4). The differences in clinical research involving medical devices in comparison to pharmaceuticals are:

- The term Clinical Investigation Plan (CIP) is generally used to refer to the study protocol in the case of a clinical investigation. *(Note: In this guidance "protocol" is used as a generic term.)*

- Randomised controlled trial designs are rarely necessary as the aims of clinical investigations are to demonstrate safety and performance. Because of this design, statistical significance may not be necessary.

- A device investigation measures the performance of the device against claims, whereas a pharmaceutical trial measures how effective a drug is in treating a particular complaint.

- The use of a medical device may sometimes be associated with a learning curve for the user, where the outcomes improve with experience.

- The methodology of testing a device performance will vary widely from study to study, due to the wide range of types of device. Some performance data might simply require user handling feedback; other data might be more analytical.

- The inventor of the device being studied might be one of the investigators.

- Effective blinding and the use of placebo are often very difficult for devices.

- The route of administration of a device is often a single surgical procedure, as opposed to repeated administration of a drug.

- By its nature, a medical device has a local effect at the point of application, as compared with the systemic effect exerted by many drugs.

- Since manufacturers may follow the literature route to CE marking, the first clinical use of a particular device may be in a post-market clinical study.

- The follow-up period for medical device studies can be much longer than for pharmaceutical trials, with studies often lasting years for implantable devices. This can often result in logistical issues in keeping in contact with trial subjects. In studies involving elderly patients the patient survival due to age may not enable full follow-up to take place.

- Data safety monitoring committees are not used routinely for device studies.

- Interim analysis of study data may be feasible (always written into the protocol and planned in advance).

- Definitions of adverse events are different which is why post-market studies on a defined cohort are performed.

7.6 Where an investigation is being conducted with a view to obtaining CE marking, RECs should be aware of the differences in the regulatory requirements, compared with the process for obtaining a marketing authorisation for a medicinal product. There is no legal requirement to demonstrate the efficacy of the device to obtain CE marking. Instead, the requirement is that the device performs according to its intended purpose as claimed by the manufacturer, and in a safe manner. This means that the follow-up time for patients may be much shorter than in studies that aim to demonstrate efficacy, and a smaller sample size is also likely to be appropriate.

7.7 The stage of obtaining CE marking through a clinical investigation is therefore not comparable to a Phase III clinical trial in drug development. It would be better likened to Phase II, where evidence of clinical activity of a medicinal product is sought rather than its efficacy.

The nature of devices trials

7.8 Comparative studies of devices are more difficult and less often undertaken. MHRA Devices encourages the industry to undertake these, but they are not usually necessary for CE marking. The required studies need to demonstrate intended performance and safety for the purpose intended.

7.9 RECs should consider the proposal before them. They may suggest improvements or ask questions to clarify the design. However, a study is not unethical if a more sophisticated study would provide more information. The subject's rights, dignity, safety or well-being are not compromised by a simpler trial. This should not be a reason for rejection.

The scope of devices trials

7.10 There is huge variety in the scope of devices research, from *in vitro* bedside testing where there are minimal risks of the study itself to material implants (heart valves, artificial joints etc). Consequently the balance of risks and benefits is extremely variable.

7.11 Therefore, more than in other ethical review it is vital to:

- identify and quantify risk

- separate risk of the interventional procedure itself (which may be part of the clinical care) and the risk of a particular device from the risk of research which may be no more than breach of confidentiality and may be assessed by another mechanism than REC review.

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8. Statistical approach

8.1 The statistical approach taken by a REC to a proposal involving a medical device will be in most respects similar to the approach needed for other types of clinical investigation. However, REC members should remember that randomised controlled studies are not standard in the medical device arena.

8.2 For clinical investigations conducted on non-CE marked investigational devices, MHRA Guidance Note 17, "Guidance notes for manufacturers on statistical considerations for clinical investigations of medical devices" (see http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=194) provides a framework for specifying the statistical elements of a clinical investigation of a device. It follows the expected elements of good design. In particular, it expects:

- a sample size calculation of the sort that will be familiar to RECs from other kinds of investigation
- primary outcome variable to be clearly specified
- null and alternative hypotheses to be stated
- the probability of Type 1 error (a false positive conclusion) to be limited to 5% or less
- a power of 80% or more.

8.3 MHRA Guidance Note 17 also advises that:

- some leeway should be allowed in case the "effect size" (as specified in the alternative hypothesis) turns out to be less than that envisaged
- an allowance for patients who do not complete the study should also be made.

8.4 The Guidance Note also discusses whether a device investigation needs a control group or not, and advises that the rationale for having or not having a control group should be made explicit in the protocol. Where the primary outcome measure can be obtained in a manner relatively free from bias, such as a radiology report, it would be possible to dispense with a control group. However, where a more subjective measure such as reduction of pain is the outcome measure, a control group would be needed. Normally this would be a "concurrent" control group, giving rise to a "parallel group" study, of a type that will be familiar to RECs who review medicinal trials.

8.5 In a "crossover" design, each patient acts as his/her own control, experiencing different treatments in two (or more) successive time periods. This design has distinct statistical advantages in circumstances where it is possible, notably a reduction in the number of patients required, as compared with a parallel group study. A crossover study could be possible for in-vitro diagnostic device studies, or in studies of external devices such as non-implantable hearing aids, but it is hard to see an application for the crossover design in a study of an implantable device, as devices are not normally

explanted unless they have failed, and to explant solely for an evaluation would be unethical.

8.6 For studies where a control group will be included, the uses of randomisation and blinding as techniques to reduce bias in an investigation may be appropriate in some circumstances. Randomisation would be expected where concurrent controls are used, and the method of randomisation should be specified. It is acknowledged that blinding of the investigator is rarely possible in studies of implantable devices. Similarly placebo-controlled implant studies are rare, since it would require the production and implantation of a placebo device or sham procedure, and this would generally be regarded as unethical. However, it may still be possible to blind a clinical evaluator, who was not involved in fitting the device, as to whether the patient was in the active or control groups. In the case of in-vitro diagnostic devices, blinding of the patient would normally be possible, and although the REC will wish to consider the ethical issues raised, these should not be insurmountable.

8.7 Where blinding is used, a method for rapidly breaking the blind in case of clinical need should be given.

8.8 MHRA Guidance Note 17 advises that the statistical analysis to be carried out should be pre-specified, in the same manner as for a medicinal trial. The use of confidence intervals around the primary and secondary outcomes measures is strongly recommended.

8.9 Some device manufacturers have used sample sizes of 10 or so, in a single group design, to demonstrate performance. However, a sample size calculation should in all cases be presented and justified. For a single-group study, the calculation should specify the width of the confidence interval to be obtained around the primary outcome measure. On occasion, the sample size may be restricted for practical reasons, such as a scarcity of patients with the condition of interest, and the sample size question in IRAS allows for such limitations to be discussed.

8.10 Obviously, applicants may also wish to carry out post-marketing studies to demonstrate long-term effectiveness and safety, and the design of these studies would be much more akin to a Phase III or Phase IV clinical trial, with follow-up over the intended lifetime of the device, which could also be the lifetime of the patient in the case of an implantable device. There is limited external guidance on the requirements for post-marketing surveillance studies, although this is available from MHRA for breast implants, heart valves and joint replacements.

8.11 Finally, it is worth remembering that, where an investigation is being conducted with a view to obtaining CE marking, MHRA has access to external statistical experts as part of its approval process. So the REC should not feel solely responsible for the review of the statistical design of a clinical investigation, and indeed should refrain from redesigning an investigation, which would be outside its role. The REC should instead assure itself that sufficient detail has been given to provide assurance that the investigation would be competently conducted, and could demonstrate its intended endpoint.

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9. Amendments

Notifications to MHRA Devices

9.1 All changes or modifications to the protocol, whether relating to the device, aspects of the study design, investigators or investigating institutions must be notified to the Competent Authority and not implemented until a letter of agreement has been obtained from the Competent Authority. All requests for change or modification to the protocol should state: the proposed change; the reasons for the proposed change; and a statement to the effect that such change(s) do not increase the risk to either the patient or user.

Notifications to the REC

9.2 Amendments are changes made to the research after a favourable ethical opinion has been given. A "substantial amendment" is defined as an amendment to the terms of the REC application, or to the protocol or any other supporting documentation (e.g. instructions for use, participant information sheet) that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the participants;
- the scientific value of the study;
- the conduct or management of the study;
- the quality or safety of any medical device used in the study.

9.3 All substantial amendments should be notified to the REC that gave a favourable opinion (the "main REC") using a Notice of Substantial Amendment form. For further guidance from NRES on the definition of "substantial" and "non-substantial" amendments, see: http://www.nres.npsa.nhs.uk/applicants/after-ethical-review/amendments/

9.4 The Notice of Substantial Amendment form is available on the NRES website at the above link and also in IRAS.

9.4 Non-substantial amendments do not need to be notified to the REC.

9.5 Where revisions are proposed to the application before an ethical opinion has been given, these should be submitted by letter rather than by a Notice of Substantial Amendment form.

9.6 The main REC has the discretion to decide whether or not a proposed amendment is substantial and requires ethical review. Chief investigators and sponsors should seek advice from the main REC if in doubt. For further information on amendments http://www.nres.npsa.nhs.uk/applicants/after-ethical-review/amendments/

Notification to NHS organisations

9.7 Where NHS permission for research has been given, notification of any subsequent amendment to the initial application should be made to NHS R&D offices at research sites in accordance with the instructions in IRAS.

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10. Safety reporting for medical devices research

10.1 In medical devices research a Serious Adverse Event (SAE) is defined as untoward occurrence that:

(a) results in death;
(b) is life-threatening;
(c) requires hospitalisation or prolongation of existing hospitalisation
(d) results in persistent or significant disability or incapacity;
(e) consists of a congenital anomaly or birth defect; or
(f) is otherwise considered medically significant by the investigator.

Notifications to MHRA

10.2 All SAEs involving a non-CE marked device under clinical investigation must be reported to MHRA (Devices Division), whether initially considered to be device related or not. Reports should also be made on SAEs occurring in the same investigation being carried out in other EU countries, since such events may have a direct influence on the conduct of the investigation in the UK.

10.3 Device-related SAEs involving a CE-marked device in a post-market surveillance study are reportable to the MHRA Adverse Incident Centre but these are reported under the requirements of the Devices Vigilance requirement, rather than the requirements for clinical investigation adverse incident reporting.

Notifications to REC

10.4 A SAE occurring to a research participant at a UK trial site should be reported to the main REC if in the opinion of the Chief Investigator the event was:

Related – that is, it resulted from administration of the medical device or any of the research procedures, and

Unexpected – that is, the type of event is not listed in the protocol as an expected occurrence.

10.5 Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the SAE report form for research other than clinical trials of investigational medicinal products (non-CTIMPs) published on the NRES website. http://www.nres.npsa.nhs.uk/applicants/after-ethical-review/safetyreports/

10.6 The Chief Investigator should include a report on the safety of participants in the annual progress report to the REC.

10.7 Individual reports of SAEs will be reviewed by the REC at a sub-committee or Committee meeting.

10.8 There is no requirement to provide reports to RECs other than the main REC.

10.9 For an overview of safety and progress reporting requirements in research other than CTIMPs, see http://www.nres.npsa.nhs.uk/applicants/after-ethical-review/safetyreports/

Notification to NHS organisations

10.10 SAEs should be reported to the relevant care organisation in accordance with local incident reporting procedures. Safety and progress reports to RECs should be copied to the relevant care organisations.

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11. Links, contact points and communications

Medical devices industry

11.1 There is a useful flowchart on Clinical Data Requirements and Clinical Research Process on the Association of the British Healthcare Industries (ABHI) website:

http://www.abhi.org.uk/multimedia/docs/regulation/clinicalresearchflowchart.pdf

11.2 The following are experts within the medical devices industry who may be able to assist with manufacturer-specific questions

Mick Borroff, Chair, ABHI/ICR/MHRA Clinical Investigations Working Group
mborroff@dpygb.jnj.com http://www.abhi.org.uk/

Janette Benaddi, Chair, Institute of Clinical Research Medical Devices sub-committee
janette@medvance.co.uk http://www.icr-global.org

Regulation of medical devices

11.3 General information on the regulation of medical devices can be found on the MHRA website at:
http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=48

11.4 Guidance on clinical investigations can be found at the following page with links to the documents listed below:
http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=194

- *Guidance Note 1: guidance notes for manufacturers on clinical investigations to be carried out in the UK.*
- *Guidance Note 3: information for clinical investigators.*
- *Guidance Note 4: pre-clinical assessment – guidance for assessors.*
- *Guidance Note 5: guidance on biocompatibility assessment*
- *Guidance Note 17: guidance notes for manufacturers on statistical considerations for clinical investigations of medical devices.*
- *Guidance: Clinical investigations under the Medical Devices Regulations 2002: health care establishments*

11.5 Specific queries relating to clinical investigation of medical devices in the UK should be directed to MHRA (Devices Division) using the contact points at the foot of the following web page:

http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=194

Ethical review of medical devices research

11.6 Queries from researchers wishing to know if their research requires ethical review should be sent to queries@nres.npsa.nhs.uk or to the Chair of a REC flagged to review research involving medical devices (see contact details at http://www.nres.npsa.nhs.uk/applicants/help/contacts/contacts.htm).

11.7 For all other queries from researchers or the general public related to the ethical review process, please contact the NRES queries line at queries@nres.npsa.nhs.uk.

11.8 Any queries from RECs should be directed initially to the appropriate REC Operational Manager, who will seek advice from NRES Head Office if necessary.

11.9 Guidance on communications between MHRA and RECs has been issued separately and is available on the NRES website at: http://www.nres.npsa.nhs.uk/rec-community/guidance/#MedicalDevicesGuidance

NHS R&D offices

11.10 For advice on applying for management permission for research, please contact the R&D office for the research site. Contact details and further guidance about R&D procedures are available at http://www.rdforum.vispa.com.

Integrated Research Application System

11.11 For guidance on completing applications in IRAS, please see the question-specific guidance linked to each question or available in collated form on the Help page at https://www.myresearchproject.org.uk/Help/Information.aspx.

11.12 For technical queries on using IRAS, please contact the IT Helpdesk at helpdesk@infonetica.net.

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12. Glossary

ABHI	Association of the British Healthcare Industries
CE Mark	Officially, CE has no meaning as an abbreviation, but may have originally stood for *Communauté Européenne* or *Conformité Européenne*. The CE mark is a mandatory European marking for certain product groups to indicate conformity with the essential health and safety requirements set out in European Directives. A "CE Mark" for any device indicates that a manufacturer has demonstrated to MHRA that the stated device complies with the relevant Essential Requirements.
Caldicott Guardian	The nominated guardian of patient information within a NHS care organisation
CAS	Central Allocation System
CI	Chief Investigator – in the REC system this refers to the investigator who submits the application to the ethics committee and has overall responsibility for the conduct of the trial. The equivalent term used by the MHRA is Principal Clinical Investigator.
CIP	Clinical Investigation Plan
Competent authority	In the UK this is the MHRA (Devices Division)
CTIMP	Clinical trial of an investigational medicinal product
ICR	Institute of Clinical Research
IRAS	Integrated Research Application System (see https://www.myresearchproject.org.uk)
Medical device	Any health care product which is used for a patient in the diagnosis, treatment, prevention or alleviation of illness or injury. "medical device" means an instrument, apparatus, appliance, material or other article, whether used alone or in combination, together with any software necessary for its proper application, which – (a) is intended by the manufacturer to be used for human beings for the purpose of- (i) diagnosis, prevention, monitoring, treatment or alleviation of disease, (ii) diagnosis, monitoring, treatment, alleviation

	of or compensation for an injury or handicap, (iii) investigation, replacement or modification of the anatomy or of a physiological process, or (iv) control of conception; and (b) does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, even if it is assisted in its function by such means, and includes devices intended to administer a medicinal product or which incorporate as an integral part a substance which, if used separately, would be a medicinal product and which is liable to act upon the body with action ancillary to that of the device;
MHRA	Medicines & Healthcare products Regulatory Agency. MHRA (Devices Division) is the Division responsible for medical devices.
NRES	National Research Ethics Service (formerly the Central Office for Research Ethics Committees)
REC	Research Ethics Committee
RES operational manager	Research Ethics Service manager responsible for providing advice and assistance to RECs in a particular area of the UK
SAE	Serious Adverse Event
SSA	Site-Specific Assessment

For a larger glossary associated with the ethical review process
http://www.nres.npsa.nhs.uk/applicants/help/glossary.htm

For a larger glossary associated with MHRA terms
http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=408

For a larger glossary associated with the medical devices industry
http://www.abhi.org.uk/glossary/default.aspx

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Annex A Taxonomy of medical device clinical studies
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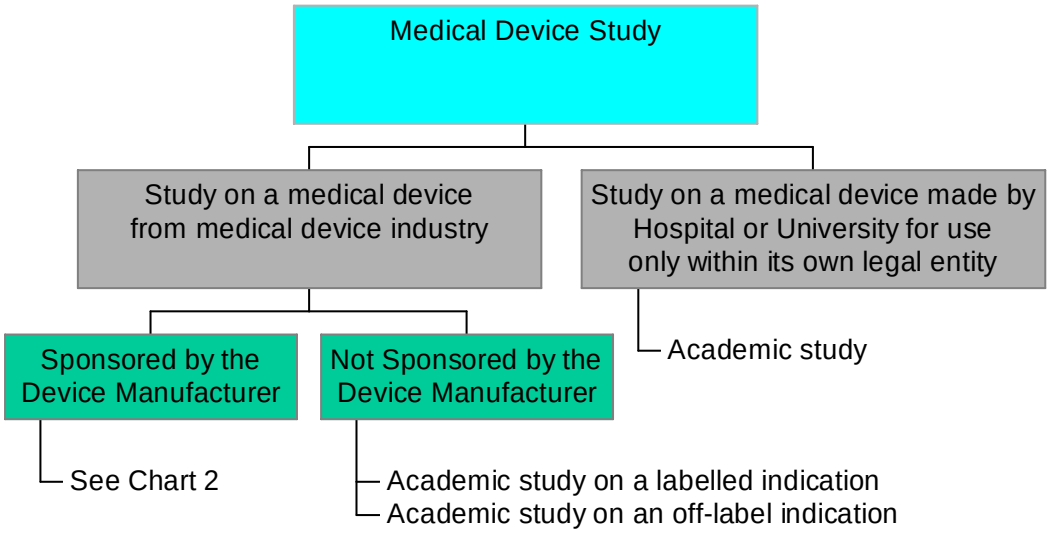
Chart 1: Medical device studies – industry or academic



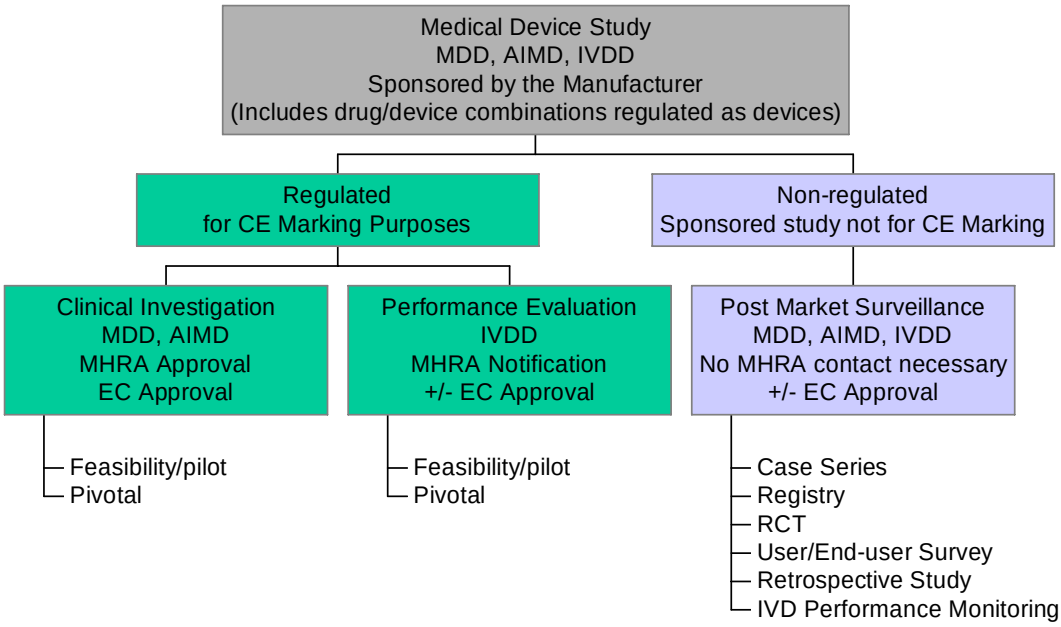
Academic Studies

Academic Study of a marketed medical device for a labelled indication	**Example**	**Ethics Approval Needed?**
Same studies as in unregulated arm of Chart 2		See Chart 2

Academic Study of a marketed medical device for an off-label indication	**Example**	**Ethics Approval Needed?**
Same study types as in unregulated arm of Chart 2	Clinician wants to study an existing device for a new indication or intended purpose without collaboration with the supplier e.g. to use a coronary artery stent in the carotid artery.	Yes

Academic Study of a "home made" medical device	**Example**	**Ethics Approval Needed?**
Same study types as in regulated arm of Chart 2	Academic department develops and manufactures a new medical device only for use in its University hospital. *N.B. Use outside its legal entity would bring the institution inside the scope of the Medical Devices Regulations 2002 and requires MHRA approval*.	Yes

Chart 2: Manufacturer sponsored device studies[2]



Post market surveillance studies

Case Series (single or multi-centre)	**Examples**	**Ethics approval needed**
Standard of Care (SOC)	Clinical audit of primary cemented hip replacement.	No
SOC + protocol driven visits in line with accepted follow-up practice	Clinical audit of primary cemented hip replacement with extra follow-up visits at 3, 5, 7, 10 years.	No
SOC + additional outcome instruments (clinician or patient administered)	Audit of primary cemented hip replacement with additional use of Oxford Hip Score, EQ5-D (administered in clinic and by post).	No
SOC + research procedures	Audit of primary cemented hip replacement with radiostereometric analysis (RSA) or blood ion levels.	Yes
Extended case studies	Prospective documentation of difficulty primary cemented hip replacement cases to understand limits to standard component use.	No
N.B. May have SOC plus additional visits + outcomes + research procedures.		

[2] N.B. Drug/device combinations regulated as medicinal products (e.g. a pre-filled asthma inhaler) do not follow this taxonomy, however drug/device combinations regulated as devices (e.g. a drug-eluting stent) will follow this classification system.

Registry (multi-centre)	Examples	Ethics approval needed
Case series of consecutive cases treated using device	Prospective registry of hip resurfacing arthroplasty.	No
Case series of consecutive cases having particular condition treated using device and comparators	Prospective registry of hip resurfacing arthroplasty and conventional primary hip replacement for OA patients aged <55 years.	No
N.B. May have SOC plus additional visits + outcomes.		

Randomised Controlled Trial	Examples	Ethics approval needed
Conventional RCT with comparator	Open vs. mini-incision total hip replacement surgery.	Yes

Device User or End-User Survey	Examples	Ethics approval needed
Device user survey	Ease of use of new instrumentation set for total hip replacement surgery. User evaluation of pressure sore management devices (mattresses or seating) for development of promotional literature.	No
Device end-user survey	Ease of use evaluation in the hands of health care professionals or laboratory personnel. Ease of use evaluation in the hands of lay users of home-use IVDs.	No

Retrospective Study	Examples	Ethics approval needed
Historical cohort collection of clinical data for off-label indications	Collecting data to review outcomes following identification of emerging new indications or method use e.g. mini-incision total hip replacement surgery or whether hip replacement patients should have anti-coagulation therapy.	No

IVDD Performance Monitoring	Examples	Ethics approval needed
SOC or SOC with additional samples donated	Accuracy check of an IVD against a laboratory reference. Check on aspects of performance such as precision, specificity, sensitivity etc.	No

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Annex B Medical device study decision tree for REC Approval and NHS permission

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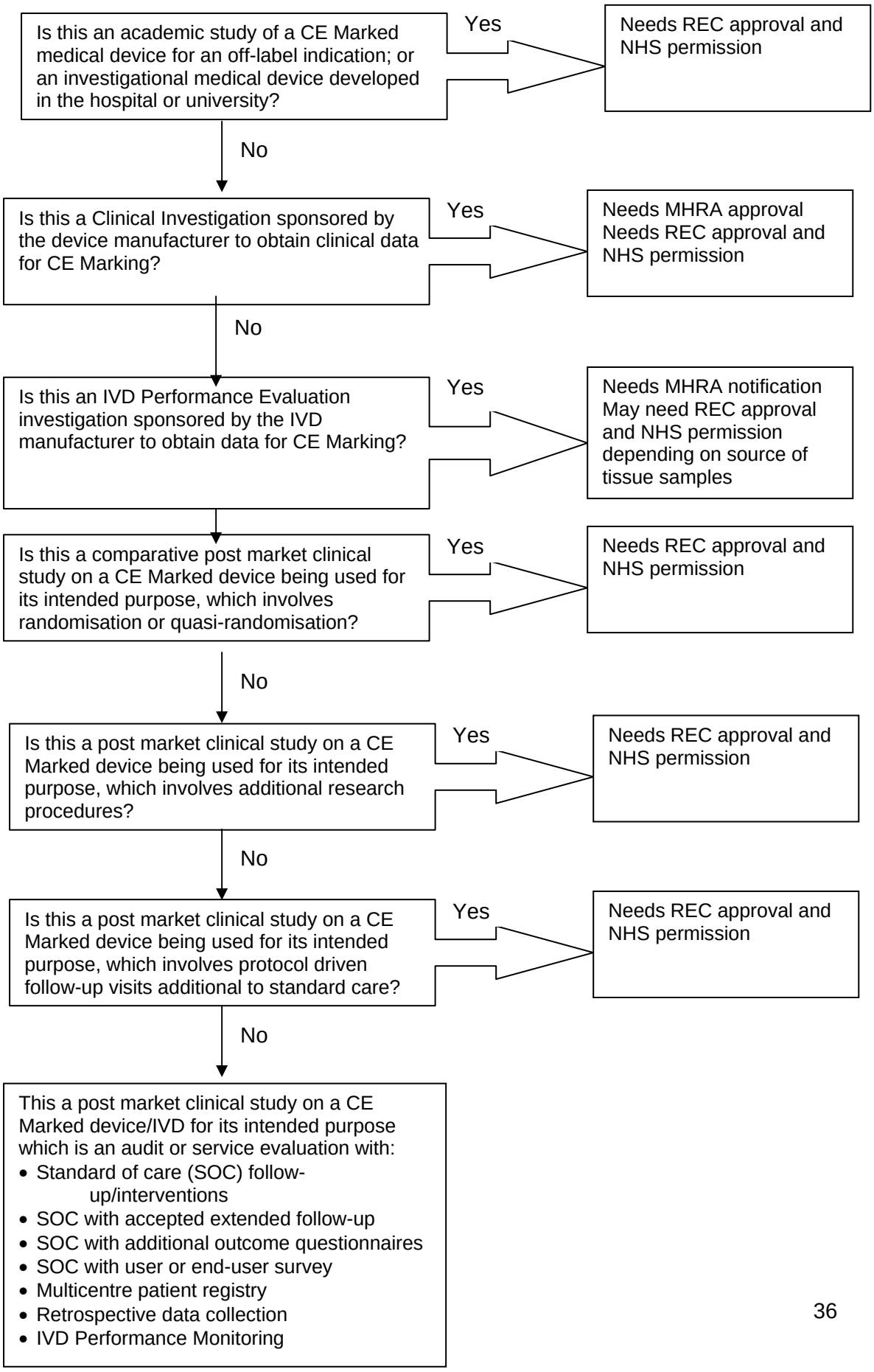

Notes and definitions

Standard of care	Generally accepted interventions and follow-up visits used in the management of such cases in audit situations
Randomisation or quasi-randomisation	Assignment to treatment by a truly random or quasi-random process
Additional research procedures	Interventions that are not used in standard treatment of the patient but are required by the research protocol such as repeated blood samples, exposure to additional radiation etc
Accepted extended follow-up	Protocol driven visits which are accepted in most participating sites of care or national standards
Follow-up visits additional to standard care	Protocol driven visits which are not accepted in most participating sites of care

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