



Medicines & Healthcare products  
Regulatory Agency



Guidance on legislation

# Clinical investigations of medical devices – guidance for manufacturers

September 2018

## Contents

Clinical investigation in the UK: requirements of the legislation .....	4
Is a clinical investigation required: the practical decisions .....	5
Clinical investigations: special circumstances .....	6
Making an application for pre-clinical assessment.....	7
The MHRA's processing of the clinical investigation .....	10
Documentation required for all submissions.....	10
Clinical investigation plan.....	13
Special features of clinical investigations .....	14
How your application will be handled by the MHRA .....	16
Amendments.....	18
Final written report .....	19
Early termination of clinical investigation.....	19
Adverse events involving devices undergoing clinical investigation.....	19
Humanitarian use of non CE-marked devices .....	20
Guidance notes for clinical investigators .....	20
Glossary of terms.....	21
Appendix 1 Flow diagrams of how the MHRA processes clinical investigations .....	23
Appendix 2 Guidance on medical devices incorporating tissues of animal origin .....	24
Appendix 2 Guidance on medical devices incorporating tissues of animal origin .....	25
Appendix 3 Guidance on medical devices which require sterilization .....	26
Appendix 4 Guidance on clinical investigations of active devices.....	27
Appendix 5 Guidance on medical devices incorporating a medicinal substance or human blood derivative having ancillary action.....	30

This document replaces Guidance Note 1 'Guidance for manufacturers on clinical investigations to be carried out in the UK'

### Revision history

This version	Date published	Changes
V1.0	October 2013	n/a
V2.0	March 2016	Revised appendix 4 – software and programmable devices
V3.0	July 2017	Revised sections 'How to apply' and 'MHRA Decision' to reflect current requirements. Plus, other minor changes.
V3.1	September 2018	Revised MHRA contact information and form name change

© Crown copyright. Published by the Medicines and Healthcare Products Regulatory Agency

## Clinical investigation in the UK: requirements of the legislation

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 of the [European directives](#). To demonstrate such compliance, it will usually be necessary to provide clinical data, which can consist of:

- a critical evaluation of the relevant scientific literature currently available relating to the safety, performance, design characteristics and intended purpose of the device, where there is demonstration of equivalence of the device to the device to which the data relates and the data adequately demonstrates compliance with the relevant essential requirements  
or
- a critical evaluation of the results of all the clinical investigations made  
or
- a critical evaluation of the combined data provided from the two bullet points above.

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 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, biological safety, population involved, conditions of use and clinical purpose.

3. However, unless safety and performance can be adequately demonstrated by other means, data generated from a specifically designed clinical investigation of a medical device are likely to be required, in particular with implantable and class III devices. 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
- determine any undesirable side effects under normal conditions of use and assess whether these constitute risks when weighed against the intended performance of the device.

4. 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 patients 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 for CE marking purposes.

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.

5. 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 their authorised representatives in the European Union) must give 60 days of prior notice to the Secretary of State for Health by writing to the UK competent authority (the MHRA). If, within 60 days of formal acceptance of the Notice, the MHRA has not given written notice of objection, the clinical investigation may proceed. The MHRA 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)).

6. 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 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 MHRA
- 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.

7. In addition, the principles of clinical investigations of medical devices are set out in the standard [BS EN ISO 14155:2011](#) Clinical investigation of medical devices for human subjects. Good clinical practice. These are harmonised standards providing presumption of conformity with Annex 7 of the Active Implantable Medical Devices Directive and Annex X of the Medical Devices Directive.

## Is a clinical investigation required: the practical decisions

8. In making a decision as to whether a clinical investigation is required, a manufacturer needs to work through a series of decisions in order to reach a conclusion.

- What are the essential requirements relevant to the device in question with which compliance must be demonstrated?
- What data are required in order to demonstrate this compliance?
- What testing is necessary to produce these data e.g. bench testing, animal testing?
- Are clinical data required to demonstrate compliance? If so, do the clinical data already exist on the device in question (published or unpublished) or by analogy with published data generated in respect of an equivalent device (see 2 above).

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

- the device is an implantable or Class III medical device
- 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 or where the materials are to be used for a significantly longer time than previously, 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.

10. In circumstances where it is unclear to the manufacturer whether there are sufficient existing clinical data to demonstrate compliance with the essential requirements in order to obtain the CE marking, discussion with the relevant notified body, where applicable, may prove helpful before embarking on the planning of a clinical investigation

11. Notification to the MHRA will not be required if the medical device to be used is CE marked for the purpose under investigation

## Clinical investigations: special circumstances

### Change in the intended use/performance claims of a device

12. Clinical data may be required in the case of a device already authorized 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 should be made to the MHRA.

### Comparative studies

13. Notification of a clinical investigation to the MHRA is not required where a device is CE-marked for the purpose intended or, in the case of a comparative study of two devices, where each has obtained prior CE marking and each is used for their original purpose. However, relevant ethics committee approval would still be required in both cases. Where at least one of the devices under study is not CE-marked, the manufacturer(s) of the non-CE marked device(s) must notify the clinical investigation to the MHRA.

### Prototype devices

14. It is recognised that a manufacturer may wish to submit a small number of 'prototype models' of a device to clinical investigation in order to assess safety and/or performance; and that such prototypes may need to undergo a number of changes prior to large-scale production. These changes will be regarded as variations included within one application unless, in the view of the MHRA, the risk to patients or users is increased by the proposed changes. Under these circumstances, the MHRA reserves the right to request a new submission in order that the safety aspects of the altered device can be given due consideration with regard to patient health and safety.

### Clinical investigations also submitted to the FDA or other non-EU regulatory authorities

15. Manufacturers should clearly indicate whether the European and non-European protocols are the same. If not, the areas of difference should be referenced and an explanation of the reasons for the differences provided. It is recognised that the objectives of a clinical investigation which is also being carried out in a country or countries outside the European Union, may be wider than those required by the Medical Devices Regulations, for example they may include efficacy or effectiveness. Changes to protocol requested by other regulatory authorities should be copied to the MHRA for information. At such times, manufacturers should indicate whether the changes instigated by the non-EU regulatory authority will also be made to the European protocol.

### **In-house manufactured medical devices**

16. Products manufactured in-house in a healthcare establishment and undergoing testing for proof of concept are not subject of the provisions of the Medical Devices Regulations provided that the device is being manufactured and used on patients within the sole legal entity. In circumstances where the in-house manufacturer sees and intends a commercial medical application in the results generated (irrespective of whether the manufacturer and subjects are part of the same legal entity) the manufacturer will need to notify the MHRA of a proposed clinical investigation. If there is any doubt as to the interpretation, contact the MHRA for clarification.

### **'Off-label' use**

17. If a clinician uses a CE-marked device for a new, 'off-label' purpose that is unsupported by the manufacturer, then the clinician and the relevant healthcare establishment may take on the responsibilities of 'the manufacturer' if they see and intend a commercial application, and must therefore fulfil all the requirements of a manufacturer as set out in the Medical Devices Regulations 2002, including notification of a clinical investigation to the MHRA. They may also take on liability with reference to the device being used 'off-label'.

## **Making an application for pre-clinical assessment**

### **Prior to making a notification/application**

18. Make sure that you have all the information necessary to demonstrate compliance with all the relevant essential requirements of the directives (except for those that are the subject of the investigation).

A very common reason for the MHRA objecting to an investigation is the failure of the manufacturer to supply the necessary data within the 60 day time period allowed by the Regulations.

Details of the information required are contained within this document and also in our other guidance documents: 'Information for clinical investigators of medical devices', 'Biocompatibility assessment' and 'Statistical considerations for clinical investigations of medical devices'.

19. We are happy to answer any questions that you may have about the UK regulatory process for clinical investigations, prior to making a notification. However, we are not able to perform a full assessment of your proposed clinical investigation protocol at this stage. You are therefore advised to contact us should you have any concerns prior to making a notification. Questions should be directed to [devices.regulatory@mhra.gov.uk](mailto:devices.regulatory@mhra.gov.uk). In some cases, where specific issues cannot be addressed in writing, a pre-submission meeting or conference call may be necessary, which we can arrange.

### **How to apply**

20. Applications **must** be made via the [Integrated Research Application System \(IRAS\)](#).

21. Send the completed Clinical Investigation Application Form and the supporting information requested on these forms to the MHRA (see section 27 below).

22. The 60 day assessment period will commence when the valid notification forms and documentation are received by the MHRA. Day 1 of the 60 days is taken as being the first working day that follows the date of receipt of a valid Notification.

23. All documentation should be sent by recorded delivery.

24. All information must be in English. If any part of the supporting data consists of material in another language, this must be translated. One copy of the original document in its original language should accompany the application.

25. You must submit 3 copies of all forms and documents, each on a separate CD. Please submit 1 extra CD for each of the following:  
where animal tissues have been utilised  
where the device is patient contacting  
where non CE marked software is being used (for stand-alone software and all devices that incorporate software)  
If your investigation includes these three factors, you will need to submit a total of 6 CDs.

All pages must be in their correct, numbered sequence, including reprints, diagrams, tables and other data.

All text and any relevant drawings and their captions must be clear and legible.

26. All documents must be arranged on the CDs as separate attachments. Include a document index on each CD and ensure that all documents are named appropriately e.g.:

- clinical investigation plan
- essential requirements checklist
- instructions for use
- investigator's brochure
- patient consent
- patient information
- risk analysis
- sterilization validation report
- summary of pre-clinical data etc.

### **Where to apply**

27. Application for pre-clinical assessment or any queries regarding an application should be directed to:

Ms Annie Dhillon  
Devices Regulatory Group  
MHRA  
10 South Colonnade  
Canary Wharf  
London  
E14 4PU  
Email [annie.dhillon@mhra.gov.uk](mailto:annie.dhillon@mhra.gov.uk) Tel: 020 3080 6886

### **Charging / fees**

28. A charge will be made by the MHRA to the manufacturer for the assessment of a proposed clinical investigation as detailed in the Medical Devices Regulations 2002: section 56 as amended by SI 2013 No 525.

On receipt of a valid notification MHRA will invoice the applicants. The relevant fee is detailed as follows:

Devices are categorised according to risk as a group A or B device:

Group A includes class I, IIa, and IIb devices, other than implantable/long term invasive

Group B includes class IIb implantable / long term invasive, class III, active implantable devices.

Fees for Group A (low risk) devices are £3,820 (initial application) or £2,920 (resubmission).

Fees for Group B (high-risk) devices are £5,040 (initial application) or £3,570 (resubmission).



Manufacturers should note that if you withdraw a notification for a clinical investigation within 5 days of the MHRA receiving it, 50% of the relevant fee will be charged. If you withdraw an investigation later than these 5 days, we will charge the full fee.

## The MHRA's processing of the clinical investigation

29. In devising its policy for the handling of clinical investigations under the provisions of the Medical Devices Directives within the UK, the aim of the MHRA is to handle all applications in the shortest time possible, whilst at the same time ensuring that any risk to the patient and user is minimised and also justified by the potential benefit to the subjects entered into the proposed clinical investigation.

30. If further information is required during the course of a clinical investigation assessment, a letter will be sent to the manufacturer requesting this information. Should the nature of the requested information be unclear, it is essential that the manufacturer contacts the MHRA as soon as possible to request clarification, or a meeting or conference call if preferred. The 60-day clock does not stop when additional information is requested. This applies in all circumstances, including notifications made that cover prolonged holiday periods such as Christmas or New Year.

### General requirements

31. Manufacturers (or their authorised representative in the EU) are required to submit initially certain information and to undertake to make available subsequently, if requested by the MHRA, information as specified 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.

32. The Clinical Investigation Application Form helps the MHRA record the applications and accompanying documentation and helps manufacturers ensure that all required information is available and referenced appropriately.

## Documentation required for all submissions

### Signed statement

33. All applications must contain a statement (Active Implantable Medical Devices Directive: Annex 6 2.2; Medical Devices Directive: Annex VIII 2.2):

- that the device in question conforms to the essential requirements except with regard to those aspects of the device that are to be investigated and that in respect of those aspects, every precaution has been taken to protect the health and safety of the patient.

By signing this statement the manufacturer is declaring that the device meets all of the relevant essential requirements, other than those subject to the investigation.

Manufacturers must therefore ensure that at the time a notification is made to the MHRA, they have all documentation required to demonstrate conformity with the relevant essential requirements available for submission to the MHRA when requested.

34. All applications must contain a statement (Active Implantable Medical Devices Directive: Annex 6 2.2; Medical Devices Directive: Annex VIII 2.2) indicating:

- whether or not the device incorporates, as an integral part, a substance or human blood derivative referred to in Section 7.4 of Annex I of the Medical Devices Directive and Section 10 of the Active Implantable Medical Devices Directive.

35. All applications submitted under the Medical Devices Directive 93/42/EEC must contain a statement (Medical Devices Directive: Annex VIII 2.2) indicating:

- whether or not the device is manufactured utilising tissues of animal origin as referred to in Directive 2003/32/EC.

**36. General Information**

- Date of submission.
- Applicant's name/address/telephone number/fax number and contact name for communication.
- Whether first submission or re-submission.
- If re-submission with regard to the same device, previous date(s) and reference number(s) of earlier submission(s).
- List other member states participating in the clinical investigation as part of a multi-centre/multinational study, details of applications to other competent authorities in the EU.
- Details of any approval or audit by a notified body or other third party of manufacturing processes at the site(s) where the device is manufactured and, if applicable, a copy of the quality certificate covering the manufacturing site.
- Confirmation of insurance of subjects.

**37. Details allowing device to be identified**

- Generic name of device.
- Model name.
- Model number(s), if any.
- Name and address of manufacturer.

**38. Other device details**

- Classification of device.
- Brief description of device and its intended use together with other devices designed to be used in combination with it.
- Design drawings, diagrams of operation and diagrams of components, sub-assemblies, circuits etc., including descriptions and explanations necessary to understand the aforementioned drawings/diagrams.
- Identification of any features of design that are different from a previously similar marketed product (if relevant).
- Details of any new or previously untested features of the device including where applicable, function and principles of operation.
- Summary of experience with any similar devices manufactured by the company including length of time on the market and a review of performance related complaints.
- Risk benefit analysis to include identification of hazards and estimated risks associated with the manufacture (including factors relating to device design, choice of materials, software) and the use of the device (ISO 14971), together with a description of what actions have been taken to minimise or eliminate the identified risk.
- Description of materials coming into contact with the body, why such materials have been chosen, and which standards apply (if relevant).
- Identification of any special manufacturing conditions required and if so how such requirements have been met.
- A description of the methods of manufacturer, in particular as regards sterilization and identification of packaging used for sterilization of device.
- A summary of the relevant standards applied in full or in part, and where standards have not been applied, descriptions of the solutions adopted to satisfy the essential requirements specified in the Active Implantable Medical Devices Regulations and the Medical Devices Regulations, as appropriate.

- The results of the design calculations and of the inspections and technical tests carried out, etc.
- Instructions for use.
- What provisions, if any, have been made by the manufacturer for the recovery of the device (if applicable) and subsequent prevention of unauthorised use?
- Photograph (preferably in colour)/diagram/sample if appropriate.
- Identification of any tissues of animal origin, as referred to in Directive 2003/32/EC, including details of sourcing and collection of the animal tissue(s) prior to manufacturing operation; and details with regard to validation of manufacturing procedures employed for the reduction or inactivation of unconventional agent; and any other risk management measures that have been applied to reduce the risk of infection (see appendix 2).
- Identification of a substance (medicinal product) or human blood derivative incorporated with the device as an integral part, and the data on the tests to be carried out to assess the safety, quality and usefulness of that substance or human blood derivative (see appendix 5).

### **39. Detailed information on the device**

The depth of detailed information supplied with the notification should be appropriate to the classification of the device, novelty of design, materials used and risks associated with the device.

- Full description of device, including a list of accessories, principles of operation and block or flow diagram of major components.
- Principal design drawings and circuit diagrams, including materials and biomaterials, together with a description and explanations necessary for the understanding of the said drawings and diagrams. If details of materials are requested, information sufficient to characterise fully the identity and chemical composition of all materials coming into patient contact, including name and address of manufacturer, trade name/code, quantitative formulations, results of chemical analyses, assessments of the effects of sterilization or other processes, or other data as appropriate, should be included.
- Detailed description of how biocompatibility and biological safety have been addressed. The risk assessment should cover the rationale for the decisions adopted. It should be apparent from the risk assessment, how hazards were identified and characterised and how the risks arising from the identified hazards were estimated and justified in relation to anticipated benefits. Particular attention should be paid to biological safety issues, especially for devices containing new materials that will come into contact with patients or where established materials are used in a situation involving a greater degree of patient contact. For example, where particularly hazardous materials, may be present in the final device, the risk assessment should indicate why solutions avoiding the hazard have not been adopted. A description of how the biological safety of the device has been evaluated should be included. This should include the identity of the person(s) responsible for the risk assessment, a summary of the data examined and the basis for the judgement that the materials are suitable for the proposed use. Further details are set out in the MHRA guidance on Biological Safety Assessment, available from the MHRA website.
- Details of the method(s) of sterilization. If the investigational devices are sterilized, the following information should be included (see appendix 3 for detailed guidance) and a sterilization Annex on IRAS should be completed. If the chosen sterilization process is by the use of moist heat (steam) then particular attention should be taken with regards to the 'standard sterilization parameters' applicable within the country where the devices are to be processed and sterilized. The appropriate sterilization qualification and validation reports should take account of these 'standard' requirements:

- specification of manufacturing environment used
  - details of any cleaning process prior to sterilization
  - method of sterilization
  - parameters of the sterilization process
  - site(s) of sterilization (if different from manufacturing site(s))
  - packaging materials used
  - summary of sterilization validation data
  - details of routine monitoring of the sterilization process (see appendix 3).
- Documentation demonstrating compliance of the device with the essential requirements with regard to electrical safety (see appendix 4).
  - Description of software, logic and constraints (if relevant).
  - Pre-clinical experimental data including results of design calculations and of mechanical and electrical tests and reliability checks, and any performance tests in animals.

## Clinical investigation plan

A copy of the clinical investigation plan and the investigator's brochure must be provided, which should include the following information:

### 40. General information

- Name(s), qualifications, address(es), of clinical investigator(s) and of principal clinical investigator for a multi-centre clinical investigation, together with summary of experience in the specialist area concerned and the necessary training and experience for use of the device in question.
- Name(s), address(es) of the institution(s) in which the clinical investigation will be conducted
- Description of intended purpose and mode of action of device
- A copy of the ethics committee opinion, whether fully or partially approved, or approved with conditions should be provided to MHRA at the time of submission if available (otherwise to follow).
- Copy of informed consent
- Reference to important relevant scientific literature (if any) with an analysis and bibliography
- Confirmation of insurance of subjects
- Copy of patient information sheet

### 41. Investigation parameters and design

- Aims and objectives of clinical investigation (bearing in mind which essential requirements are being addressed by the Clinical Investigation in question).
- Type of investigation i.e. whether the use of a controlled group of patients is planned.
- Number of patients (with justification).
- Duration of study with start and finish dates and proposed follow-up period, (with justification).
- Criteria for patient selection.
- Inclusion and exclusion criteria.

- Criteria for withdrawal.
- Description of the generally recognised methods of diagnosis or treatment of the medical condition for which the investigational testing is being proposed.
- Details of any proposed post-market clinical follow-up plan.

#### **42. Data collection/analysis/statistics**

- Description of end points and the data recorded to achieve the end points, method of patient follow-up, assessment and monitoring during investigation.
- Description of procedures and details of data to record and report serious adverse events and adverse device related incidents.
- Description and justification of statistical design, method and analytical procedures.

## **Special features of clinical investigations**

#### **43. Number of devices proposed for clinical investigation**

In assessing risks to health or safety, one of the areas that will be particularly considered by the MHRA is the proposed number of devices to be included within a clinical investigation. The number must be sufficient in order to demonstrate performance satisfactorily and to reveal significant risks to patients' health and safety. At the same time the number should not be so great as to place at risk more patients than necessary at a time when third party assessment of device-related risks has not been carried out. The number, therefore, should reflect the aims of the investigation, taking into account the perceived risk of the device and comply with relevant medical devices standards where appropriate. We also have a guidance document '[Statistical considerations for clinical investigations of medical devices](#)'.

#### **44. Clinical investigation duration**

The duration of a clinical investigation of a medical device should be such as to permit the demonstration of performance over a period of time sufficient to represent a realistic test of the device, and allow identification and risk assessment of any associated unacceptable adverse incidents over that period of time, allowing conclusions to be drawn as to the likely performance in the longer term. It is neither feasible nor desirable to perform a clinical investigation lasting the projected lifespan of many devices. Indeed, it is recognised that for a number of devices, e.g. orthopaedic implants and vascular stents, the majority of associated adverse incidents may not become clinically obvious for a number of years and that the clinical investigation in question will only demonstrate major short term safety problems. The duration of a clinical investigation and follow up period must be in line with relevant medical device standards where appropriate.

#### **45. Post-market clinical follow-up**

The Medical Devices Directive (Annex X) and Active Implantable Medical Devices Directive (Annex 7) require manufacturers to actively update their clinical evaluation with data obtained from post-market surveillance. It is intended that long-term safety problems be identified either under Medical Devices Vigilance or through a means of specifically designed post-market clinical studies, either extending the pre-market clinical investigation; or by studying a relevant and identified cohort of patients over a defined period of time; or through means of a specifically designed registry. Where post-market clinical follow-up is not deemed necessary, this must be duly justified and documented. In general, devices should follow a post-market clinical follow-up when one or more of the following criteria are identified:

- Innovation, where the design of the device, the material, the principles of operation, the technology or the medical indication is new.
- Severity of the disease.

- Sensitive target population.
- Risky anatomical location.
- Well-known risks associated with a similar marketed device.
- Well-known risks identified from the literature.
- Identification of an acceptable risk during pre market clinical evaluation, which should be monitored in a longer term and/or through a larger population.
- Identification of emerging risks in similar products.
- Obvious discrepancy between the pre-market follow-up windows and the expected life of the product.

#### **46. Type of investigation**

The majority of clinical investigations of medical devices under the provisions of the Medical Devices Regulations 2002 will not include a control group. The decision as to whether a control group is necessary however, will depend on the aims of the investigation. For some devices it would only be possible to demonstrate claims adequately by comparison with a separate or untreated group. If control groups are necessary however, these should be randomised and prospective, except in exceptional and justifiable circumstances.

#### **47. End points**

Care should be taken in choosing endpoints to ensure that this will support the stated aims and objectives of the clinical investigation under normal conditions of use. Methods of supporting the demonstration of these endpoints should, as far as possible, be objective, e.g. derived from the results of diagnostic or in vitro diagnostic tests, rather than be subjective, e.g. severity of symptoms.

#### **48. Labelling**

All devices intended for clinical investigation must bear the wording 'exclusively for clinical investigation' (Medical Devices Directive: Annex 1, para 13.3(H) and the Active Implantable Medical Devices Directive: Annex 1, 14.1). It is recognised that such wording may cause confusion to clinical staff in that it may be thought that the clinical investigation being referred to is of a patient rather than the device. It is therefore recommended that manufacturers draw this requirement to the attention of all clinical investigators, requesting that such investigators ensure that the meaning of this wording is clearly understood by all staff using or coming into contact with the device being investigated and that the device under investigation is segregated, where possible, from any similar devices in routine use. If a device under clinical investigation has been CE-marked for another purpose, explanatory labelling to this effect should be attached to the device under investigation.

#### **Research ethics committee opinions**

49. For all clinical investigations of devices falling within the scope of the Medical Devices Regulations, a relevant Research Ethics Committee (REC) opinion is required (Medical Devices Regulations 2002: Paragraph 16(3), section 29(2)). This opinion may be obtained in parallel with the MHRA notification. If the REC opinion is not provided at least 60 days prior to the intended clinical investigation, it should be forwarded to the MHRA as soon as it becomes available. No clinical investigation of a non-CE-marked device should be started until both the relevant REC opinion and the MHRA have raised no grounds for objection.

50. The MHRA does not accept approvals from independent ethics committees. Manufacturers should seek the opinion of a National Research Ethics Service (NRES) appointed ethics committee in all cases unless they can demonstrate a reason why NRES appointed committees would not assess their clinical investigation. In such cases the manufacturer will need to demonstrate that any independent ethics committee appointed was constituted in line with NRES guidelines. However please note that NRES will review all clinical investigations due to be conducted outside

of the NHS and therefore situations where an independent ethics committee is required are not foreseen.

51. REC approval is required from just one REC, irrespective of the number of centres participating in the clinical investigation. Further advice on how to apply for a REC opinion can be obtained from the National Research Ethics Service (NRES) at the website: <http://www.nres.npsa.nhs.uk/applications/>. There is also specific guidance for applicants at: <http://www.nres.npsa.nhs.uk/applications/guidance/>. If you require further advice email NRES Queries Line on [queries@nationalres.org.uk](mailto:queries@nationalres.org.uk).

When your application is complete, it is recommended that you book a REC which is trained to review medical device applications via the NRES Central Allocation System (CAS) Tel: 0845 270 4400. Manufacturers should make it clear, when contacting NRES, that the investigation involves a non-CE marked medical device.

Where the MHRA raises no grounds for objection to the investigation in question proceeding, the investigation may only commence once REC approval has been granted, and a copy of the REC approval letter is sent by the manufacturer to the MHRA.

52. On occasions it may be helpful for the MHRA to liaise with the relevant ethics committee concerning notifications. Additionally, it can also be helpful for the MHRA to send the Ethics Committee a copy of their final decision for information purposes. The Clinical Investigation Application Form enables the manufacturer to provide authorisation allowing such communication.

## How your application will be handled by the MHRA

### Initial receipt of documentation

53. On receipt of the documentation the MHRA will take action as shown in the flow chart in appendix 1.

54. If all the necessary documentation required as part of the original submission is complete, a letter will be sent to the manufacturer including the following:

- an acknowledgement of receipt of the notice
- a reference number for the notice which should be quoted in all communications made to the MHRA pertaining to that application
- the starting date for the notification period.

55. If the necessary documentation is incomplete, the manufacturer will be contacted as soon as possible so that the missing information can be forwarded to the MHRA. The sixty-day assessment clock will start when a complete notification has been received.

### Expert assessors

56. Copies of the documentation pertaining to a proposed clinical investigation, will then be sent to one or more assessors who have expert knowledge of aspects of clinical investigation of devices which may include clinical aspects, biocompatibility, biological safety, clinical research, immunology, pharmacology, statistics, sterilization, technology of the device, toxicology, etc.

57. Assessors from outside the MHRA will have signed a statement of confidentiality incorporating a declaration of any conflict(s) of interest. In addition, every effort will be made to ensure that no conflict of interest will arise for an expert assessor in relation to any aspect of the clinical investigation that he/she is asked to assess by the MHRA. In the interests of confidentiality however, manufacturers may, at the time of the original submission, name the institutions/individuals whom they may not wish to act as assessors for the investigation in



question. The MHRA will, so far as possible, bear such views in mind when appointing assessors. All assessors will be required to return to the MHRA all submitted documentation which they have received and to retain no copies. The MHRA will then return the documentation to the manufacturer, or destroy all documentation on the manufacturer's wishes, except for one copy which will be retained for record purposes.

### **Additional information**

58. Each expert assessor will be allowed 14 days in which he/she will be able to request, through the MHRA, any further information that he/she thinks necessary in order for a proper assessment of the proposed clinical investigation to be made with regard to his/her area of expertise. This additional information may comprise either part or the whole of the information which the manufacturer must undertake to keep available for the MHRA (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). It is in the interests of the manufacturer to supply this additional information as soon as possible if it is requested, so that an adequate assessment of all relevant data can be completed. The 60 day clock will not stop whilst this requested information is being assembled.

### **MHRA decision**

59. If, after consideration of all the evidence provided, the MHRA considers that there are no grounds relating to health or safety or public policy whereby the proposed clinical investigation should not proceed, the MHRA will notify the applicant of this decision.

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

61. Unjustifiable risks to public health or safety may include the following circumstances:

- where there are reasonable grounds to suspect that a device does not satisfy relevant essential requirements; or
- where there are reasonable grounds to suspect that the clinical investigation is not subject to controls equivalent to the requirements of the relevant European Standard (ISO 14155 parts 1 and 2); or
- where there exists expert professional opinion on the proposed clinical investigation that the risk benefit analysis given by or on behalf of the manufacturer is inaccurate and that, were the investigation to take place, there would be a significant probability of serious illness, injury or death to the patient or user; or
- where there is inadequate/incomplete pre-clinical or animal data in order to make it reasonable for clinical testing to commence, or
- where insufficient information has been submitted to enable a proper assessment of the safety aspects of the proposed clinical investigation to be made; or
- where the manufacturer has delivered any documentation necessary for the assessment so late that insufficient time remains within the 60-day notification period for the MHRA to complete its assessment.

62. If the MHRA raises grounds for objection, it will notify other EU Competent Authorities and the European Commission of the decision and grounds for objection. The grounds for objection will otherwise remain confidential between the expert assessors, the manufacturer, and the ethics committee if authorisation has been given for the latter case by the manufacturer.

63. The applicant may re-submit revised documentation pertaining to the proposed clinical investigation, provided the reason for refusal of the original application has been addressed. An appropriate fee, as defined in the Medical Devices Regulations 2002 (SI No 618) will need to accompany the subsequent notice addressing the grounds for objection and a copy of the full documentation along with the completed Clinical Investigation Application Form via IRAS should be provided. Any further questions or issues raised by the MHRA will only be in relation to the information supplied to address the original grounds for objection. This, however, is only valid provided the documentation remains the same with the exception of that addressing the grounds for objection, unless the further information raises safety issues or a significant change to the risk/benefit analysis which impinge on the original protocol. Therefore, a covering letter should be provided with the resubmission stating that the documentation does not differ from that provided with the original submission or as amended during the 60 days, except in sections that address the original grounds for objection.

When making a resubmission please provide:

1. Any necessary documents to address the grounds for objection including red lined (showing changes being made) and clean copies of all amended study documentation;
2. A covering letter stating that the documentation does not differ from that provided with the original submission or as amended during the 60 days, except in sections that address the original grounds for objection. Please include in the covering letter an explanation as to how the grounds for objection have been addressed within the documentation;
3. A revised Clinical Investigation Application Form ;
4. A copy of the original notification documentation (with the exception of those documents revised in 1 above) for reference only.

64. Manufacturers are advised to arrange a meeting or conference call with the MHRA prior to re-drafting a clinical investigation resubmission to ensure that they understand the original concerns. This provides an opportunity to discuss possible means of addressing the grounds of objection.

65. Fees for resubmission are set out in section 28 of this document (Medical Devices Regulations 2002: Section 56).

## Amendments

66. All proposed changes to the investigation whether relating to the device, aspects of the clinical investigation plan, investigators or investigating institutions must be notified to the MHRA and not implemented until a letter of agreement has been obtained from the MHRA. All requests for amendments should include the following information:

- the MHRA reference number
- the proposed change(s) to the clinical investigation plan/design of device/other study documentation
- the reason for the change(s)
- a signed statement by or on behalf of the manufacturer that the proposed change(s) do not predictably increase the risk to the patient, user or third party.

67. The MHRA retains the right to request a new clinical investigation notification if the amendments are thought to increase the risk to either the patient or the user, or if the MHRA considers that the amendments constitute a new investigation in accordance with Regulation 56(3) (Medical Devices Regulations 2002).

## Final written report

68. Manufacturers are required to notify the MHRA when a clinical investigation comes to an end (Medical Device Regulations 2002: Section 16(11) and Section 29(10)). The MHRA may request a copy of the final written report of a clinical investigation of a device falling within the scope of the Medical Devices Directive (Medical Devices Regulations 2002: Section 16(10) and Section 29(9)). It is likely that a copy would particularly be requested under certain circumstances, e.g. where a serious adverse event has occurred associated with a CE-marked device which had undergone clinical investigation authorised by the MHRA, or where a novel technology has been investigated.

## Early termination of clinical investigation

69. Manufacturers are required to notify the MHRA of the early termination of a clinical investigation and provide a justification for the early termination (Medical Device Regulations 2002: Section 16(10) and Section 29(9)). The MHRA may request a copy of the final written report of a clinical investigation of a device falling within the scope of the Medical Devices Directive (Medical Devices Regulations 2002: Section 16(10) and Section 29(9)).

## Adverse events involving devices undergoing clinical investigation

70. Regulation 16(10)(a) of the Medical Devices Regulations 2002 (SI 618) and Annex X of the Medical Devices Directive 93/42 require manufacturers to record fully all adverse events and report all serious adverse events occurring in all participating centres to the MHRA.

A 'serious adverse event' is one which:

- a) led to death
- b) led to serious deterioration in the health of the subject, that either resulted in;
  - 1) a life-threatening illness or injury, or
  - 2) a permanent impairment of a body structure or a body function, or
  - 3) in-patient or prolonged hospitalization, or
  - 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- c) led to fetal distress, fetal death or a congenital abnormality or birth defect

**Note** Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

71. All serious adverse events, whether initially considered to be device related or not, involving a device under clinical investigation coming within the scope of the Medical Devices Directive and undergoing clinical investigation, should be reported to the MHRA (Medical Devices Directive: Annex X, Para 2.3.5 and Active Implantable Medical Devices Directive: Annex 7, Para 2.3.5). Such events also include those arising out of the same investigation being carried out in other countries since such events may have a direct influence on the status of the investigation. These reports should initially be made as soon as possible and should not be delayed while the manufacturer attempts to gain access to, or test, the device or make a full investigation. The results of the full investigation should be made available later as appropriate.

72. MEDDEV 2.7/3 provides guidance on the requirements for reporting serious adverse events with timelines and provides a template form to use for this purpose. When using the Excel template to report serious adverse events, please send the completed spreadsheet to the MHRA via email at [aic@mhra.gsi.gov.uk](mailto:aic@mhra.gsi.gov.uk)

73. In the case of a blinded control clinical investigation using a CE marked device as control, all adverse events should be reported to MHRA in line with the requirements above.

74. Where an un-blinded controlled clinical investigation is being carried out using a CE marked device as the control, adverse events involving the CE marked devices should be reported to the MHRA in line with vigilance guidelines.

75. The MHRA has the right to withdraw a written notice of no objection if, in its opinion, the serious adverse events give rise to issues of public health (Medical Devices Regulations 2002: Section 16(7) and Section 29(6)).

## Humanitarian use of non CE-marked devices

76. The use of individual non-CE-marked devices falling within the scope of the Medical Devices Regulations may be authorised by the MHRA on humanitarian grounds, provided that the MHRA is satisfied that this would be in the interests of the patient and the protection of health. In such cases, the device may not be used until an application requesting such use has been made by the manufacturer and due authorisation has been given by the MHRA. The MHRA's authorisation applies only to the use of the individual device for a named individual within the United Kingdom. Failure to comply with these requirements constitutes a criminal offence.

To apply for humanitarian use of a non CE-marked device the manufacturer and clinician must fill in a form, which is on [this web page](#).

## Guidance notes for clinical investigators

77. The MHRA has other guidance documents relevant to clinical investigations: '[Information for clinical investigators](#)' and '[Statistical considerations for clinical investigations of medical devices](#)'.

Any queries regarding this document or the clinical investigation procedure should be directed to [devices.regulatory@mhra.gov.uk](mailto:devices.regulatory@mhra.gov.uk)

## Glossary of terms

### **Active implantable medical device**

means any active medical device which is intended to be totally or partially introduced, surgically or medically, into the human body or by medical intervention into a natural orifice, and which is intended to remain after the procedure.

### **Active medical device**

means any medical device relying for its functioning on a source of electrical energy or any source of power other than that directly generated by the human body or gravity.

### **Adverse device event**

means a device-related adverse incident.

### **Adverse incident**

means any undesirable clinical occurrence in a subject whether it is considered to be device-related or not.

### **Clinical investigation**

means any systematic investigation or study in human subjects, undertaken to verify the safety and performance of a device, under normal conditions of use.

### **Clinical investigation plan**

means a document that includes detailed information on the rationale, aims and objectives, design and proposed analyses, methodology, and conduct of the clinical investigation.

### **Clinical investigator**

means the person responsible for the conduct of a clinical investigation and who takes the responsibility for the health and safety of the subjects involved.

### **Device intended for clinical investigation**

means, within the context of this document, any device intended for use by an appropriately qualified practitioner when conducting clinical investigations in an adequate clinical environment.

### **Implantable device**

means any device which is intended to be totally introduced into the human body, or to replace an epithelial surface or the surface of the eye, by surgical intervention and which is intended to remain in place after the procedure. Any device intended to be partially introduced into the human body through surgical intervention and intended to remain in place after the procedure for at least thirty days is also considered an implantable device.

### **Invasive device**

means a device which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body. A body orifice includes any natural opening in the body, as well as the external surface of the eyeball, or any permanent artificial opening such as a stoma.

### **Research ethics committee**

means an independent and properly constituted body of medical professionals and non-medical members whose responsibility is to ensure that the health, safety and human rights of the patients participating in a particular clinical investigation are protected.

### **Medical device**

for the purposes of the Active Implantable Medical Devices Directive:

means any instrument, apparatus, appliance, material or other article, whether used alone or in combination together with any accessories or software necessary for its proper functioning, intended by the manufacturer to be used for human beings in the:

diagnosis, prevention, monitoring, treatment or alleviation of disease or injury;  
investigation, replacement or modification of the anatomy or of a physiological process;  
control of conception;

and which does not achieve its principal intended action by pharmacological, chemical, immunological or metabolic means, but which may be assisted in its function by such means.

### **Medical devices**

for the purposes of the Medical Devices Directive:

means any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease;
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap;
- investigation, replacement or modification of the anatomy or of the physiological process;
- control of conception

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

### **Multicentre investigation**

means a clinical investigation, conducted according to a single clinical investigation plan, which takes place at different investigation sites.

### **Performance of device**

means the action of a device with reference to its intended use when correctly applied to the appropriate subjects.

### **Relevant essential requirements**

means such of the essential requirements, or such aspects of the essential requirements as apply to a device, not including, in the case of a device intended for clinical investigation, such of those requirements, or aspects of them, as are the subject of the investigation.

### **Serious adverse incident**

Means an adverse incident that:

- led to death;
- led to a serious deterioration in the health of the subject that resulted in life threatening injury or illness; resulted in a permanent impairment of a body structure or function; required in-patient hospitalisation or prolongation of existing hospitalisation; or resulted in medical or surgical intervention to prevent permanent impairment to body structure or body function;
- led to fetal distress, fetal death or a congenital abnormality or birth defect.

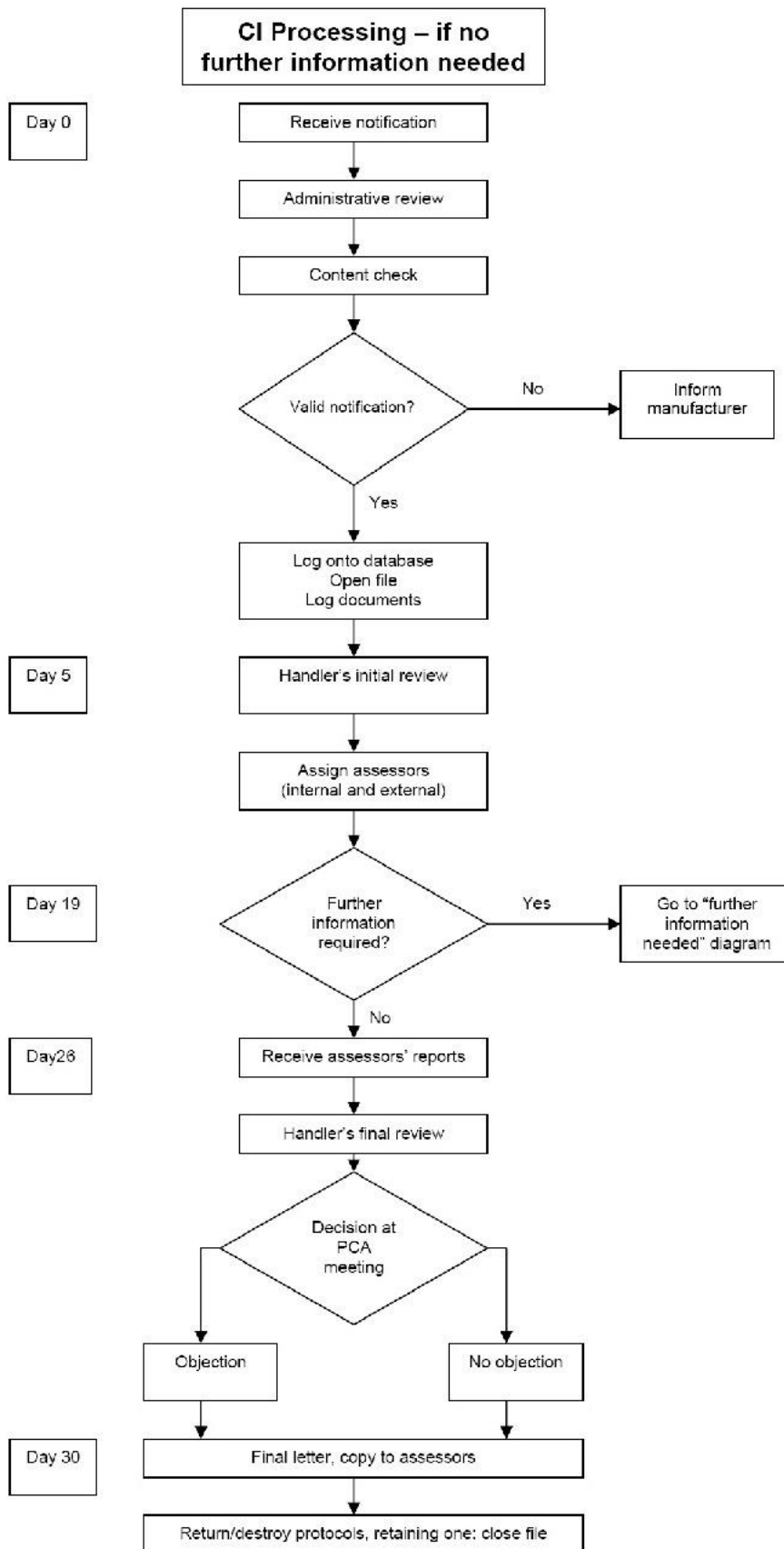
### **Subject**

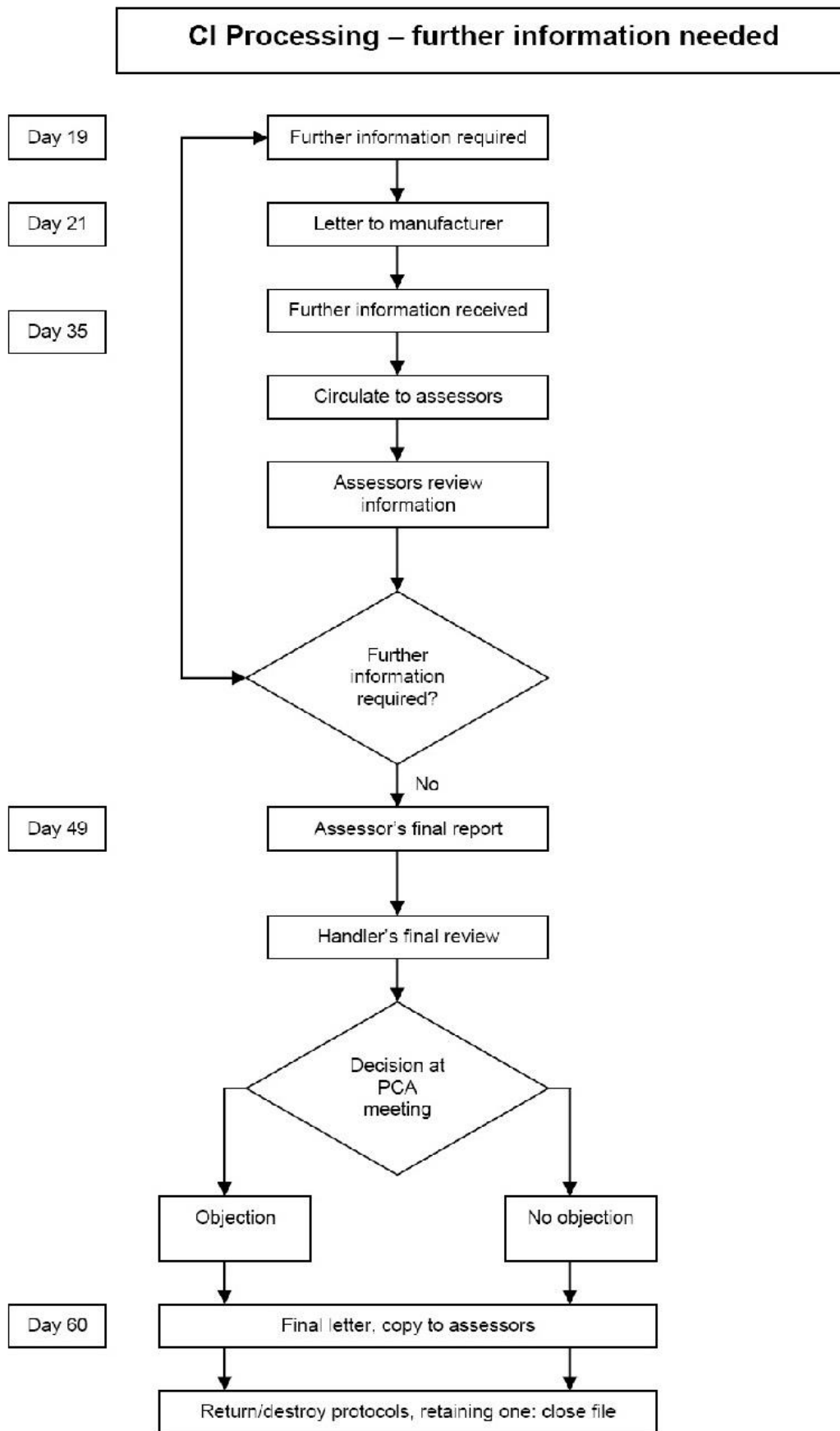
means a human being, who is either a patient or a non-patient volunteer, participating in a clinical investigation.

### **Surgically invasive**

means an invasive device which penetrates inside the body, other than through an established body orifice, with the aid or in the context of a surgical operation.

## Appendix 1 Flow diagrams of how the MHRA processes clinical investigations







## Appendix 2 Guidance on medical devices incorporating tissues of animal origin

The following additional information should be provided as part of the clinical investigation submission.

- A clear, justified statement on the decision to use animal tissues or derivatives, the expected clinical benefit, the evaluation of similar materials of animal origin and other synthetic alternatives that achieve the desired product characteristics and intended purpose.
- An overview and assessment of the key elements adopted in the risk management to minimise the risk of infection including the:
  - availability of suitable alternatives
  - selection procedures and systems for sourcing the tissue / derivative
  - details of the production processes and animals used
  - source country including the assessment of geographical risk
  - nature of the starting materials
  - systems for inactivation or removal of transmissible agents
  - quantity of animal starting tissues or derivatives required to produce one unit of medical device
  - tissues or derivatives of animal origin coming into contact with the patients and users, and the route of application
  - practices of post-market surveillance system including gathering and assessment of new information of the potential risks arising from the use of the end product.

## Appendix 3 Guidance on medical devices which require sterilization

The MHRA requires manufacturers of sterile devices, which are either provided sterile or sterilized at the point of use, to submit suitable documentation to demonstrate that the method of sterilization renders the device sterile.

If provided sterile, this should include where appropriate:

- the method of sterilization
- details of the sterilization facility, name, location, process
- proof of validation to demonstrate that the sterilization process can be delivered effectively and reproducibly to the specified devices in the sterilization load, e.g. results, certificates and justification for the choice of sterilization process
- details of the records for product release (indicator testing, dosimetric release, parametric release), this should include the results and outcomes
- data relating to bioburden, e.g. nature, frequency and outcome
- details of any environmental precautions undertaken on the device during manufacture or sterilization. Information to include; nature, frequency of monitoring and outcome
- details of any standards applied to the any of the sterilization processes.

If devices are to be sterilized at the point of use, this should include where appropriate:

- a copy of the instructions for decontamination (i.e. cleaning, disinfection and or sterilization) including details of any special precautions for handling
- appropriate validation data to demonstrate that the processes can be delivered effectively and reproducibly to the specified devices must be provided.

The Clinical Investigation Application Form (available through IRAS <https://www.myresearchproject.org.uk/>) contains sterilization questions. These questions have been designed to assist manufacturers in setting out the information required by the MHRA as a basis of assessment of sterilization of the investigational device(s).

### Important points to note

- The sterilization questions should be completed for **each** investigation device (non-CE marked) which requires sterilization. This includes any instruments or accessories.
- Where devices are sterilized at the point of use, and moist heat (steam) is chosen as the method of sterilization, particular attention should be taken with regards to the 'standard sterilization parameters' applicable within the country where the devices are to be processed and sterilized. The appropriate sterilization qualification and validation reports should take account of these 'standard' requirements.

## Appendix 4 Guidance on clinical investigations of active devices

This appendix should be read in conjunction with appendices 2, 3 and 5 of this document and the MHRA's document '[Biological safety assessment](#)' guidance document.

The following information should be provided as part of the clinical investigation submission to support claims of compliance with the essential requirements of the Council Directive, e.g. 93/42/EEC or 90/385/EEC. It is therefore necessary that the device under investigation has been manufactured and tested for safety and performance prior to an application being made to the MHRA.

### General

1. Essential requirements checklist detailing how these requirements have been addressed, including references to harmonised standards as appropriate.

Note: The application of harmonised standards is voluntary and applicants may choose alternative methods of demonstrating compliance with the essential requirements. For example, compliance with international, national or in-house standards. This should be supported by a risk benefit analysis, preferably to EN ISO 14971.

2. Documentary evidence supporting compliance with any of the standards referenced. This may include certification by an independent body, or test house. Alternatively, self-certification is acceptable, providing this is supported with evidence of design input and subsequent in-house verification.
3. For those applicants choosing self-certification against EN 60601-1 (which includes protection against electric shock hazards, mechanical hazards, fault conditions, constructional requirements, etc) a checklist for that standard, or equivalent, should be provided. This should be completed and signed by a competent engineer. Where clauses are considered not applicable, a justification should be given. Where measurements of leakage currents are made, the values should be recorded.
4. When the medical device is to be used with other devices as part of a system, e.g. connection to laptop computers, etc an additional EN 60601-1-1 checklist or equivalent covering the whole system under investigation should also be provided.

### Specialist technologies including: infra-red, laser, microwave, MRI, RF ultrasound, ultraviolet, X-ray etc.

5. Details of how this technology has been incorporated in the design and what steps have been taken to assure the safe application in the device. Information pertaining to output power, justification of safety limits used and reference to appropriate standards should be included, e.g. the relevant part 2 of the EN 60601 series.

### Active Implants

6. A summary of the Failure Mode, Effects [and Criticality] Analysis (FMEA/FMECA).
7. The results of animal studies.
8. Performance statistics and adverse incident data of earlier model, when device is the next generation of an earlier design.

## Software and programmable devices

Where the device includes a software component the following should be addressed in the notification:

### Standards compliance

MHRA strongly recommends the use of harmonised standards in the development of software. Compliance with EN IEC 62304 gives the presumption of conformity with many of the relevant essential requirements of the Directive. If the standard is not applied, objective evidence showing the software is in conformance with the corresponding essential requirements must be provided. EN IEC 62304 represents the current state of the art and as such shall be used by MHRA as a frame of reference for assessing the objective evidence supplied.

### Describe any standards used in the development of the software (e.g. EN IEC 62304, IEC 80002, IEC 80001-1).

- If EN IEC 62304 has been employed please specify the Safety Classification of all the software according to that standard.
- Provide any certification where available (testing laboratories can assess compliance with EN IEC 62304 and issue a certificate under the accreditation of ISO/IEC 17065).
- If EN IEC 62304 has not been employed please provide objective evidence showing the software is in conformance with the corresponding essential requirements.

### Describe the role of the software including whether:

- The normal operation, initial setting up, maintenance, calibration, adjustment, or monitoring of the medical device, depend on software.
- The correct operation of the medical device depends on the execution of the software within a limited time i.e. real time software is used.
- Any part of the medical device's software can be run independently on hardware not directly connected to the medical device.

### Describe the relationship of software to safety including:

- Does essential performance depend on software? (Essential performance is the performance whose absence would pose a threat of harm to the patient).
- Which risk control measures depend on software? Specify or provide a reference to supporting documentation with evidence that the software risk control measures have been implemented and tested and that they are effective.
- Is there a method of intervening in the event of a software failure?
- How would an operator detect a software failure so that they could take appropriate action?

### Describe the risk management of software including:

- A risk management process that includes software items.
- Identification of software defects, or classes of software defects, that could expose patients or operators to hazards.
- Hardware risk control measures that are used to prevent the consequences of software defects. Specify the software defects and provide evidence that the hardware risk control measures have been implemented and tested and that they are effective.

- Any use of the software development process as a risk control measure.
- Any software verification or software validation that is used as a risk control measure (verification = 'did we do the thing right', validation = 'did we do the right thing?').

**Describe the software development processes including:**

- Documentation of the system and software architecture in such a manner that it is possible to reason about the contribution of each component and software item to safety.
- Testing of software units (the lowest level of software decomposition) before integration into larger software items.
- The software design and development processes used to translate software design requirements into software implementation.

**Describe the purpose of the clinical investigation with regard to:**

- Whether the clinical investigation is intended to evaluate the fitness for clinical purpose of any part of the software and, if so, how this will be done.
- Detail of any specific protocols designed to evaluate the operation of the software in the clinical context.

**Describe the human interface including:**

- The user interfaces (mechanisms intended to allow humans to interact with the software) that the software has (including user interfaces for the patient, clinical technician, physician, service engineer, etc.).
- The target population for each type of user interface (for example, age, expertise, language, etc) and whether this is documented.
- The tests that have been done prior to the clinical investigation to evaluate the effectiveness of the user interfaces for each target population, or how this will be evaluated in the study.
- The measures used to ensure that only appropriate people are allowed to operate each different type of user interface.

**Describe how the software is protected including:**

- Protection from accidental or unauthorised change.
- Identification of roles which have the authority to make software changes during the clinical trial.
- The measures that are in place to ensure that software changes do not adversely affect the clinical investigation.

**Describe any legacy software**

- Document the version of any legacy software and provide a rationale for the continued use of the Legacy software.
- Provide evidence of any risk management activities associated with the continued use of legacy software.

## Appendix 5 Guidance on medical devices incorporating a medicinal substance or human blood derivative having ancillary action

### Additional information required with regard to the medicinal substance and/or the human blood derivative:

- Intended purpose within the context of the device and the risk analysis.
- Source, product licence (where applicable), quantity/ dosage of the medicinal component, and the method by which the substance is incorporated into the device.
- Method of manufacture (solvents/reagents used in processing, residuals).
- Qualitative and quantitative tests carried out on the medicinal substance.
- Stability data in relation to the expected shelf-life/ lifetime of the device.
- Clinical documentation (clinical data demonstrating the usefulness of the medicinal substance)

### Additional information required with regard to the medicinal substance only:

- Control of the starting materials
  - (medicinal substance specifications e.g. summary of the European Drug Master File, reference to European Pharmacopoeia or national monograph of a European Member State).
  - Manufacturers may wish to cross-reference a granted Clinical Trial Authorisation (CTA).
  - Please refer to 'The rules governing Medical Products in the European Community' volume III, Addendum II.
- Toxicological profile (summary of results of toxicity testing / biological compatibility).
  - This should include the effect on reproductivity, embryo/fetal and perinatal toxicity and the mutagenic / carcinogenic potential of the medicinal substance.
- Pharmacodynamics of the medicinal substance in relation to the device.
- Pharmacokinetic characteristics (local/ systemic exposure patterns, duration and maximum exposure and the maximum plasma concentration peak taking into account individual variability).
  - New active substances should address the release of the substance from the device, its subsequent distribution and elimination.
- Local tolerance (particularly where the route of exposure is different to the conventional application) e.g. the results of EN/ISO 10993 testing, or a review of scientific literature.

### Additional information required with regard to the human blood derivative only:

- Control of the starting materials
  - control of plasma source e.g. summary of the European Plasma Master File,
  - production of the blood derivative
  - Manufacturers may wish to cross-reference a granted Clinical Trial Authorisation (CTA) or marketing authorisation for a medicinal product.
- Pharmacodynamics of the medicinal substance in relation to the device.