



Medicines & Healthcare products  
Regulatory Agency



Guidance on legislation

Clinical investigations of medical devices –  
compiling a submission to MHRA

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This document replaces the 'Checklist of required documents' and should be read in conjunction with 'Clinical investigations of medical devices – guidance for manufacturers'.

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V1.0		n/a

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## Submitting a clinical investigation for MHRA assessment

### Prior to making a notification/application

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 as part of the clinical investigation submission are contained within this document and also in our other guidance documents: 'Information for clinical investigators of medical devices', 'Biological safety assessment' and 'Statistical considerations'. The information detailed in this document 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.

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 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

1. Applications **must** be made via the [Integrated Research Application System \(IRAS\)](#).
2. Complete the Clinical Investigation Application form on IRAS and upload the relevant supporting documents onto IRAS. Follow the instructions on IRAS on how to submit the application.
3. The 60 day assessment period will commence once a valid notification is 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. Validation will be confirmed within 5 working days and where a notification is found to be invalid the 60 days will not commence.
4. All information must be in English. If any part of the supporting data consists of material in another language, this must be translated before submission.

Applicants should ensure that complete copies of all documents are provided and all information is provided in a readable format (i.e. not too small to see full rows and ensure no text is truncated). All text and any relevant drawings and their captions must be clear and legible.

5. Documents should ideally be provided in pdf format and, where possible, be searchable. Therefore do not include pdfs of scanned documents.

**Where to apply**

Any queries regarding the submission process on IRAS should be directed to the Clinical Investigations Unit at: [devices.regulatory@mhra.gov.uk](mailto:devices.regulatory@mhra.gov.uk)

**MHRA fees**

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.

The relevant fee should be paid upon receipt of an invoice from MHRA.

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.

Current fees are detailed on the [MHRA website](#)

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

## IRAS Form and supporting documentation required

### MHRA Devices submission checklist on IRAS

The Checklist tab on IRAS contains a list of all documents that should be included in the submission to MHRA:

- Covering letter on headed paper
- Clinical investigation plan
- Investigator's brochure
- Participant information sheet
- Participant consent form
- CVs for UK clinical investigators
- Device details
- Essential requirements checklist
- Risk analysis
- Instructions for use of a medical device
- Device labels
- Summary of all bench testing and pre-clinical testing conducted
- Summary of all clinical experience with the device to date
- End of study reports for any concluded clinical investigations that involved the same medical device under investigation
- List of standards met
- Sterilisation validation report (where relevant)
- Software information (where relevant)
- Biological safety assessments of patient contacting materials (where relevant)
- Information on animal tissues (where relevant)
- Information on any medicine or human blood derivative incorporated into the device
- Research ethics committee opinion (if available)

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.

### **Documentation required for all applications**

#### **1. Covering letter on headed paper**

As a minimum, your cover letter should include the following information:

- an explanation of the purpose of the clinical investigation
- confirmation of whether the study is First In Human, Pilot/Feasibility or Pivotal and provide the rationale and justification for this
- confirmation of whether the study has commenced in other countries. Where this is the case provide details of the status/duration and known outcomes of the study to date
- confirmation of whether the same device has been the subject of previous notifications to MHRA
- MHRA reference numbers for any previous notifications
- confirmation of whether any subsequent modifications have been made to the device or whether the device remains unchanged from the previous notifications
- If you are submitting a new application to address a previous application where MHRA gave grounds for Objection, please:

- Provide detailed information on how you addressed the grounds for objection
- Clearly identify which documentation is the same as the previous submission
- Where amended documentation has been provided, please provide a tracked-changes version and a clean version.

## 2. Clinical Investigation Plan

A copy of the clinical investigation plan must be provided, which should be in line with ISO14155.

The following information should either be included in the Clinical Investigation Plan or within other documents submitted to MHRA

- Name(s), address(es) of the institution(s) in which the clinical investigation will be conducted
- A signed copy of the signature page for the Clinical Investigation Plan signed by all UK investigators
- Description of intended purpose and mode of action of device

### 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. A clear description of the type of study design (e.g. single-arm or controlled, parallel group or crossover) and purpose of the study (feasibility vs confirmatory).
- If applicable, details of the type of randomisation to be used (e.g. simple, block, stratified, minimisation). If stratified randomisation or minimisation is used, the stratification/minimisation variables should be listed.
- If applicable, the study classification e.g. a superiority trial (to show that the test device is superior to the comparator), an equivalence trial (aiming to show that two treatment arms only differ by an amount which is clinically unimportant), or a non-inferiority trial (to demonstrate that the test device is not clinically inferior to the comparator).
- If applicable, details of the approach to blinding (double-blind, single-blind or open label with justification).
- Sample size (with justification) - see section 1.2 of the MHRA guidance on [statistical considerations](#). Even in a first-in-human or pilot/feasibility study which does not propose to test a formal hypothesis it should be justified that the proposed sample size is suitable for the purpose of the study.
- Number of centres participating in the study with justification.
- Duration of study with start and finish dates and proposed follow-up period, (with justification).
- Criteria for patient selection including: Inclusion and exclusion criteria (with justification and any age limits specified), 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.
- Where applicable, details of any proposed post-market clinical follow-up plan and provision of long-term safety and performance data of the device under investigation

### Data collection/analysis/statistics

- Description of end points (primary and secondary) and the data recorded to achieve the end points, method of patient follow-up, assessment and monitoring during investigation.
- The analysis populations to be used.
- The hypotheses which are to be tested and/or the device performance characteristics which are to be estimated in order to satisfy the objectives of the clinical investigation. The statistical methods to be used to accomplish these tasks should be described for the primary (and preferably the secondary) variables.
- The significance level to be used for any statistical tests, and whether this is 2-sided or 1-sided.

- Methods for handling missing data should be stated, with sensitivity analyses to assess the impact of missing data, if appropriate.
- Description of all interim analyses planned and their timing and purpose (e.g. stopping for futility or efficacy). Details of the statistical analysis of the interim data, along with precise rules for which actions will be taken and the results that would lead to those actions (e.g. the trial will be stopped for efficacy if 2-sided  $p < 0.001$  at the interim analysis). Details of how the type I error of the final analysis will be adjusted to account for the interim analysis. In the case of unblinded interim analyses, details of how dissemination of the results will be restricted to preserve the integrity of the trial.
- Description of procedures and details of data to record and report serious adverse events and adverse device related incidents (in line with requirements in MEDDEV 2.7/3).
- Please also refer to MHRA guidance on [statistical considerations](#) for further details

### 3. Clinical Investigator's Brochure

A copy of the investigator's brochure must be provided, which should be in line with ISO14155.

The following information should either be included in the Investigator's Brochure or within other documents submitted to MHRA

- Reference to important relevant scientific literature (if any) with an analysis and bibliography
- Classification of device with rationale.
- 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.
- Photograph (preferably in colour).
- Details of any comparable device on the market
- 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.
- Summary of the 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 sterilisation and identification of packaging used for sterilisation 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.
- What provisions, if any, have been made by the manufacturer for the recovery of the device (if applicable) and subsequent prevention of unauthorised use? Including procedures for analysis of implantable devices following explant.
- Identification of any tissues of animal origin

- Identification of a substance (medicinal product) or human blood derivative incorporated with the device as an integral part.
- Details of training for users (both healthcare professionals and patients)

#### **4. Participant information sheet**

Participant information should identify and explain all risks to participants.

#### **5. Participant consent form**

#### **6. CVs for the UK clinical investigators**

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 clinical studies and in the specialist area concerned and the necessary training and experience for use of the device in question.

#### **7. Device details**

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.

- Detailed description of device, how the device is assembled and how the constituent parts are joined together
- A list of accessories, principles of operation and block or flow diagram of major components.
- Principal design drawings and circuit diagrams, together with a description and explanations necessary for the understanding of the said drawings and diagrams.
- A picture or schematic illustration of the device operation and photos of the device.
- A video demonstrating the operation of the device if available.
- For device systems provide a summary of how compatibility of all device components (whether CE marked or not) has been determined, including an updated risk analysis covering this.
- For CE marked devices being used as 'ancillary' devices within the study:
  - Ensure the devices are being used in accordance with the CE marked instructions for use;
  - Provide evidence that the safety profile of such devices has been assessed to ensure there are no current safety concerns. This assessment should, as a basic step, involve a search of any safety notices published by the manufacturer or MHRA.

#### **8. Essential Requirements Checklist**

- Essential requirements checklist detailing how these requirements have been addressed, including references to harmonised standards as appropriate.
- Include evidence of how applicable standards have been met.
- Include copies of all test reports and other documents referenced in the essential requirements checklist within the submission to MHRA.

#### **9. Risk Analysis**

- Provide a risk analysis preferably to EN ISO 14971.
- For device systems the risk analysis should cover compatibility of all device components (whether CE marked or not).

#### **10. Instructions for use of medical device**

Required for all investigational device components. Should include where relevant, information on setup of the equipment for use with a patient and any pre-use checks that may be required



## 11. Device Labels

Copies of the labels for the investigational device (these should state that the device is for clinical investigation only)

## 12. Summary of all bench testing and pre-clinical testing conducted

- a summary of all bench testing conducted, the results obtained and the manufacturer's conclusions with details of which device model and version was involved. Include a justification for choice of each bench test performed, reference to the specific standard where the test is stipulated (where relevant) and whether the test has been adapted in any way.
- Where equivalence is claimed, provision of supporting data should cover the clinical, technical and biological aspects of the device in line with [MEDDEV 2.7.1](#)
- Results of design calculations
- Acceptance criteria for testing e.g. tensile strength and stiffness
- Confirmation of whether each device will be individually tested for conformance to the design criteria after manufacture
- a summary of all testing conducted in animals or *ex vivo*, the results obtained and the manufacturer's conclusions. Include a justification for the number and species of animals used and any non-animal models tested. For implantable devices include detail on the condition and integrity of the device at explant and histopathological results. Studies conducted should be in accordance with ISO 10993.
- a summary of any testing conducted to address human factors and usability engineering. See MHRA guidance on [Human Factors and Usability Engineering](#).

## 13. Summary of clinical experience with the device to date

This should include adverse events seen and performance related complaints, including number of complaints of each type and the root cause in each case.

Confirmation of whether the device involved was identical to the investigational device intended to be used in the proposed clinical investigation. If not, provide full details of how the new device differs. Detail changes to the design, materials, intended use and the rationale for these changes. Provide information on all First In Human and Pivotal Trials, irrespective of the place and time of the study and the results.

## 14. List of standards met

- list of all harmonised standards that the device complies with including year of issue.
- If the standard(s) are only met in part, please provide a description of solutions adopted to meet the essential requirements of the MDD.
- Provide a full justification for where the standards met have been superseded
- 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. Please provide a full justification where such alternative methods have been chosen.

## 15. 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).

## Documentation required in specific circumstances

### 16. Sterilisation validation report

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

The Clinical Investigation Application form on IRAS has been designed to assist manufacturers in setting out the information required by the MHRA as a basis of assessment of sterilisation of the investigational device(s).

If the investigational devices are sterilised, the following information should be included:

- the method of sterilisation
- details of the sterilisation facility, name, location, process
- details of the records for product release (indicator testing, dosimetric release, parametric release), this should include the results and outcomes
- details of any standards applied to the any of the sterilisation processes.
- A sterilisation validation report for each component including:
  - a. Proof of sterilisation validation protocols and processes to demonstrate that the sterilisation process can be delivered effectively and reproducibly to the specified devices in the sterilisation load, e.g. validated results, certificates, standards, risk assessments, and justification for the choice of sterilisation process
  - b. Details of appropriate methods for bioburden determinations e.g. type (nature), frequency, results and outcome;
  - c. Details of microbiological environmental precautions undertaken on the devices during manufacture or sterilisation e.g. type of controls, frequency of monitoring, results and outcome

If devices are to be sterilised at the point of use, the following information should be included where appropriate:

- a copy of the instructions for decontamination (i.e. cleaning, disinfection and or sterilisation) 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.

#### Important points to note

- Where devices are sterilised at the point of use, and moist heat (steam) is chosen as the method of sterilisation, particular attention should be taken with regards to the 'standard sterilisation parameters' applicable within the country where the devices are to be processed and sterilised.

The appropriate sterilisation qualification and validation reports should take account of these 'standard' requirements:

- specification of manufacturing environment used
- details of any cleaning process prior to sterilisation
- method of sterilisation
- parameters of the sterilisation process
- site(s) of sterilisation (if different from manufacturing site(s))
- packaging materials used
- summary of sterilisation validation data
- details of routine monitoring of the sterilisation process.

## 17. Software information

For medical devices that include a software component (either stand-alone software or software incorporated into a medical device) the following should be addressed in the notification:

The Clinical Investigation Application form on IRAS has been designed to assist manufacturers in setting out the information required by the MHRA as a basis of assessment of software.

Please provide copies of all documents referenced in the answers given to the software questions in the Clinical Investigation Application form.

Please provide documentation to demonstrate that the software has been developed in accordance with its safety classification. At a minimum the following is necessary:

- Software Development Plan
- Risk Management Plan and Report – specifically including the software hazard analysis.
- Software Configuration Management Plan
- Software System Requirements Specification
- Software System Verification Plan and Report
- Documented Software Problem Resolution Process.
- Evidence of review of completeness for software release

For stand-alone software, please ensure the whole system is considered and hazards caused by the platform/hardware the software is run on are addressed.

## 18. Biological safety assessment of patient contacting materials

Required for all investigational devices that are patient contacting.

- 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 guidance document Biological Safety Assessment available from the MHRA.
- 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 sterilisation or other processes, or other data as appropriate, should be included.
- Haemocompatibility risk assessment (all endpoints should be considered including haemolysis, thrombosis, coagulation, platelet activation and the working of the complement system).
- Please refer to MHRA guidance on [biological safety assessment](#)

## 19. Information on animal tissues

For medical devices incorporating tissues of animal origin the following information should be provided:

- 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 and validation of these
  - any other risk management measures that have been applied to reduce the risk of infection
  - 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.

## 20. Information on any medicine or human blood derivative incorporated into the device

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

- Intended purpose of the inclusion of the medicinal substance in the context of the device and the risk analysis.
- Source, marketing authorisation (where applicable) and the quantity/ dosage of the medicinal substance, incorporated into the device.
- Method of manufacture (solvents/reagents used in processing, residuals).
- Qualitative and quantitative tests carried out on the medicinal substance in the device.
- Stability data in relation to the expected shelf-life/ lifetime of the device. Patient information regarding storage of the device should be included.
- Clinical documentation (clinical data demonstrating the usefulness of the medicinal substance).

Additional information required with regard to the medicinal substance only:

- Control of the medicinal substance
  - medicinal substance specifications e.g. summary of the European Drug Master File, EDQM Certificate of Suitability, 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).
  - 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 human blood derivative
  - 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 human blood derivative in relation to the device.

## 21. Active devices

For active medical devices the following information should be provided within the Device Details or the Summary of all bench testing and pre-clinical testing conducted:

- 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.
- 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.
- 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.
- Details (with diagrams) of: how the battery is sited within the device, the earthing to ensure patient-user safety, earth leakage current, whether the devices incorporate electrical and thermal fuses, battery consumption indicator, audible/visual low battery alert, audible/visual battery error alert, other audible/visual error alerts

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

The following information should be provided within the Device Details or the Summary of all bench testing and pre-clinical testing conducted:

- 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.

## 23. Active Implants

For active implantable medical devices the following information should be provided within the Device Details or the Summary of all bench testing and pre-clinical testing conducted:

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