How to submit a clinical investigation for a non CE marked device or a CE marked device for a new purpose to the MHRA

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<td>Version 4.0</td>
<td>08 Feb 2010</td>
<td>Formation of JRCO</td>
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<td>Version 5.0</td>
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<td>Annual Review</td>
</tr>
<tr>
<td>Version 6.0</td>
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<td>Scheduled Review</td>
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<tr>
<td>Version 8.0</td>
<td>25 Oct 2017</td>
<td>Scheduled Review</td>
</tr>
</tbody>
</table>
# Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. <strong>Purpose</strong></td>
<td>3</td>
</tr>
<tr>
<td>2. <strong>Introduction</strong></td>
<td>3</td>
</tr>
<tr>
<td>2.1 Is it a device?</td>
<td>3</td>
</tr>
<tr>
<td>3. <strong>Procedure</strong></td>
<td>4</td>
</tr>
<tr>
<td>3.1 Making an application for pre-clinical assessment</td>
<td>5</td>
</tr>
<tr>
<td>3.2 How to apply</td>
<td>5</td>
</tr>
<tr>
<td>3.3 Where to apply</td>
<td>6</td>
</tr>
<tr>
<td>3.4 Cost of applying</td>
<td>6</td>
</tr>
<tr>
<td>3.5 How to make a payment to MHRA</td>
<td>7</td>
</tr>
<tr>
<td>3.6 Documentation required</td>
<td>11</td>
</tr>
<tr>
<td>3.7 Additional considerations</td>
<td>12</td>
</tr>
<tr>
<td>3.8 MHRA processing of approval application</td>
<td>14</td>
</tr>
<tr>
<td>3.9 Changes or modifications to the protocol</td>
<td>14</td>
</tr>
<tr>
<td>3.10 Final written report</td>
<td>14</td>
</tr>
<tr>
<td>3.11 Adverse incidents involving devices undergoing clinical investigation</td>
<td>14</td>
</tr>
<tr>
<td>3.12 Humanitarian use of non-CE-marked devices</td>
<td>14</td>
</tr>
<tr>
<td>4. <strong>References</strong></td>
<td>15</td>
</tr>
<tr>
<td>5. <strong>Appendices</strong></td>
<td>17</td>
</tr>
<tr>
<td>Appendix 1</td>
<td>17</td>
</tr>
<tr>
<td>Appendix 2</td>
<td>18</td>
</tr>
<tr>
<td>Appendix 3</td>
<td>21</td>
</tr>
<tr>
<td>Appendix 4</td>
<td>22</td>
</tr>
</tbody>
</table>
1. PURPOSE

This Standard Operating Procedure (SOP) describes the procedure for seeking MHRA approval to conduct a clinical investigation for a non-CE marked device or a CE marked device for a new purpose.

It should be used in conjunction with JRCO/SOP/002 ‘Ethics Approval for Health-Related Research, JRCO/SOP/003 on ‘Applying for NHS REC Approval’ and the JRCO/SOP/039 ‘Health Research Authority for Research Studies’

2. INTRODUCTION


A copy of the directive can be found on the Europa website.

A number of additional Directives amending the original Directive have since been introduced; further details can be found on:

These regulations establish systems under which a manufacturer must submit to the UK Competent Authority for approval for clinical investigations of medical devices to be carried out in the UK. The UK Competent Authority is the Medicines and Healthcare products Regulatory Authority (MHRA), please see https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency). The aims of these regulations are to ensure the safety and performance of medical devices, and to prohibit the marketing of devices that might compromise the health and safety of patients, users or any relevant 3rd party.

2.1 Is it a device?

In the Medical Devices Directive (MDD), a medical device is described as any instrument, apparatus, appliance, software, material or other article used alone or combined for humans to:

- diagnose, prevent, monitor, treat or alleviate disease
- diagnose, monitor, treat, alleviate or compensate for an injury or handicap
- investigate, replace or modify the anatomy or a physiological process
- control conception

A medical device does not achieve its main intended action by pharmacological, immunological or metabolic means although it can be assisted by these.
If manufacturing a medical device, the specific directive for the product type must be followed as it sets out the essential requirements the product must meet in the interest of patient safety. Further information on what a medical device is can be found in the MDD.

See the guidance on borderline products if you are unsure whether your product is a medicine or a medical device or if it overlaps:

https://www.gov.uk/guidance/decide-if-your-product-is-a-medicine-or-a-medical-device

3. PROCEDURE

Manufacturers wishing to make an application for pre-clinical assessment of an active implantable medical device or a medical device to be carried out in part or in whole in the UK should apply to the MHRA. Under the UK regulations, in order to be able to CE mark any device, a manufacturer must demonstrate that the device complies with the relevant essential requirements by carrying out a conformity assessment. The assessment route depends on the classification of the device. Clinical data is normally provided to demonstrate compliance, which can take the form of either:

- A compilation of the relevant scientific literature currently available on the intended purpose of the device and the techniques employed. This should be accompanied by a critical evaluation of the scientific literature where appropriate; or
- The results and conclusions of a specifically designed clinical investigation.

More details of this process are available in appendix 4 - Medical devices: conformity assessment and the CE mark.

Prior to submitting a notification to the Competent Authority, you are advised to ensure that you have the information necessary to demonstrate compliance with all the relevant essential requirements except for those that are the subject of the investigation. You will need to supply the necessary data within the 60 day time period allowed by the Regulations.

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 object on grounds relating to public health or public policy.

For guidance on whether a Clinical Investigation is required to demonstrate compliance of the device with requirements, the MHRA’s Guidance for Manufacturers on Clinical Investigations to be carried out in the UK should be consulted via the website https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/632175/Guidance_for_mfrs_on_clinical_trials_July_2017.pdf.
3.1 Making an Application for Pre-Clinical Assessment

It is strongly advised that before submitting a notification to the MHRA, you have all the necessary information to demonstrate compliance with all the relevant essential requirements (except for those that are the subject of the investigation). A high percentage of the grounds for objection are due to failure to provide the necessary data within the 60 day time period allowed by the regulations.

3.2 How to Apply

Applications for approval for a clinical investigation of a medical device should be made via the Integrated Research Application System (IRAS) which is accessed via the website https://www.myresearchproject.org.uk and completing forms PCA1 and PCA2, together with the supporting information requested on these forms. Data is collected through IRAS system, which captures the data/information needed by MHRA offering the facility for users to print out PCA1 and PCA2 forms and sterilization proforma for signing before making a notification to the MHRA. For full guidance on completing these forms the MHRA website should be consulted regularly for up to date information (https://www.gov.uk/topic/medicines-medical-devices-blood/clinical-trials-investigations)

Notifications will only be accepted by the MHRA once the signed forms, necessary supporting documentation and the appropriate fee have been received by the Agency.

Queries regarding the application process can be made to the Medical Devices Unit at the MHRA via Daniella Smolenska (Daniella.Smolenska@mhra.gsi.gov.uk) or by telephone on 020 3080 7363.

PCA1 is a computer input form. PCA2 is a reference index to assist manufacturers in ensuring that all required information is available and referenced properly.

All documentation submitted must be clearly labelled “documentation only” and sent by recorded delivery. Three copies of all forms and documents, each on a separate CD must be submitted and all pages must be in their correct numbered sequence (including reprints, diagrams, tables and other data). All information should be provided in English and if any part of the supporting data consists of material in another language, this must be translated, with one copy of the document in its original language accompanying the application. One extra CD for each of the following must be submitted: 1) where animal tissues have been utilised; 2) where the device is patient contacting; 3) 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 documents should be arranged on the CDs as separate attachments and named appropriately (e.g.: clinical investigation plan, investigator's brochure, patient information sheet, patient consent form). There must be a document index on each CD.

If further information is requested by the MHRA, a letter will be sent to the manufacturer requesting this information. The 60-day clock does not stop when additional information is requested.

The Integrated Research Application System (IRAS) found at: https://www.myresearchproject.org.uk/ combines the ethics application along with
forms PCA1, PCA2 and the sterilisation proforma, thereby alleviating the need to complete two separate sections. The resulting form from IRAS can be submitted to the MHRA in the way described below.

3.3 Where to Apply
Applications for pre-clinical assessment or any queries regarding an application should be directed to:

Daniella Smolenska
Regulatory Affairs Manager (Medical Device Clinical Trials)
Floor 4 orange zone
151 Buckingham Palace Road
London, SW1W 9SZ
Tel: 020 3080 7363.

3.4 Cost of Applying
A charge applies for the pre-clinical assessment of clinical investigation notifications by the MHRA, with the fees for re-notification* in the event of an objection. This charge is made by the MHRA to the manufacturer for the assessment of a proposed clinical investigation. Devices are categorised according to risk into one of four classes according to whether they are considered low (class I) medium (class IIa, IIb) or high (class III) risk and the costs will be determined by the class of the device:

- Class I, IIa, or IIb other than implantable or long-term invasive: £3,820 (£2,920)*
- Class IIb implantable or long-term invasive, Class III, and active implantable: £5,040 (£3,570)*

* figures given in brackets denote re-notification fees

Please refer to the MHRA website for up-to-date costs.

3.5 How to make payments to the MHRA:
If paying by cheque, please make payable to MHRA

Remittance advices should be marked for the attention of the Cashier, and forwarded to:

MHRA Accounts Receivable
5th Floor
151 Buckingham Palace Road
London
SW1W 9SZ

Or email: sales.invoices@mhra.gov.uk,

Bank details for payment by bank transfer,

Account name: MHRA
3.6 Documentation Required

3.6.1 Signed Statement
All applications must contain a signed statement stating that the device in question conforms to the essential requirements except with regard to those aspects of the device that are to be investigated in the study, and that in respect of those aspects, every precaution has been taken to protect the health and safety of the patient.

3.6.2 General Information

i. Date of submission
ii. Applicant's name/address/telephone number/fax number and contact name for communication
iii. Whether first submission or re-submission
iv. *If re-submission with regard to the same device, previous date(s) and reference number(s) of earlier submission(s)
v. *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
vi. *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
vii. Confirmation of insurance of subjects

* = Additional information that may be requested by the MHRA should they deem it necessary

3.6.3 Details allowing device to be identified

i. Generic name of device
ii. Model name
iii. Model number(s), if any
iv. Name and address of manufacturer

3.6.4 Other device details
i. Classification of device

ii. Brief description of device and other devices designed to be used in combination with it.

iii. Design drawings, diagrams of operation and diagrams of components, sub-assemblies, circuits etc., including descriptions and explanations necessary to understand the aforementioned drawings/diagrams.

iv. Identification of any features of design that are different from a previously similar marketed product (if relevant).

v. Details of any new or previously untested features of the device including where applicable, function and principles of operation.

vi. 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.

vii. 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 (ISO14971), together with a description of what actions have been taken to minimise or eliminate the identified risk.

viii. Description of materials coming into contact with the body, why such materials have been chosen, and which Standards apply (if relevant).

ix. Identification of any tissues of animal origin incorporated within the device together with information on the 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 agents, along with any other risk management measures that have been taken to limit the infection risk.

x. Identification of any special manufacturing conditions required and if so how such requirements have been met.

xi. Identification of packaging used for sterilisation of device.

xii. 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.

xiii. Instructions for use.

xiv. What provisions, if any, have been made by the manufacturer for the recovery of the device (if applicable) and subsequent prevention of unauthorised use.

xv. Photograph (preferably in colour)/diagram/sample if appropriate

xvi. Identification of a 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
xvii. The results of design calculations and of the inspections and technical tests carried out.

3.6.5 Clinical Investigation Plan General Information

i. 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.

ii. Name(s), address(es) of the Institution(s) in which the clinical investigation will be conducted

iii. Description of intended purpose and mode of action of device

iv. A copy of the Ethics Committee opinion, whether fully or partially approved, or approved with conditions

v. Copy of informed consent

vi. Reference to important relevant scientific literature (if any) with an analysis and bibliography

vii. Confirmation of insurance of subjects

viii. Copy of Patient Information Sheet

3.6.6 Investigation Parameters and Design

i. Aims and objectives of clinical investigation (bearing in mind which Essential Requirements are being addressed by the Clinical Investigation in question).

ii. Type of investigation i.e. whether the use of a controlled group of patients is planned.

iii. Number of patients (with justification);

iv. Duration of study with start and finish dates and proposed follow-up period, (with justification).

v. Criteria for patient selection;

vi. Inclusion and exclusion criteria;

vii. Criteria for withdrawal;

viii. Description of the generally recognised methods of diagnosis or treatment of the medical condition for which the investigational testing is being proposed.

ix. Details of any proposed post-market clinical follow-up plan

3.6.7 Data Collection/Analysis/Statistics

i. Description of end points and the data recorded to achieve the end points, method of patient follow-up, assessment and monitoring during investigation.

ii. Description of procedures and details of data to record and report serious adverse events and adverse device related incidents.

iii. Description and justification of statistical design, method and analytical procedures.
3.6.8 Documentation to be Kept Available

It is important that 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. The following information may therefore be provided if appropriate, and should always be available for the MHRA if they request it:

i. Full description of device, including a list of accessories, principles of operation and block or flow diagram of major components.

ii. 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 sterilisation or other processes, or other data as appropriate, should be included.

iii. Description of manufacturing methods.

iv. 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.

v. Identification of any tissues of animal origin, 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.

vi. Details of the method(s) of sterilisation. If details of sterilisation are requested, the following information should be included. Where this information has not been included within the main body of the clinical investigation notification the sterilisation proforma should be completed.
   a. - specification of manufacturing environment used;
   b. - details or any cleaning process prior to sterilisation;
   c. - method of sterilisation;
   d. - parameters of the sterilisation process;
   e. - site(s) of sterilisation (if different from manufacturing site(s));
   f. - packaging materials used;
   g. - summary of sterilisation validation data;
   h. - details of routine monitoring of the sterilisation process
vii. Documentation demonstrating compliance of the device with the Essential Requirements with regard to electrical safety.

viii. Description of software, logic and constraints (if relevant).

ix. Pre-clinical experimental data including results of design calculations and of mechanical and electrical tests and reliability checks, and any performance tests in animals.

x. Details of medicinal substances acting ancillary to the medical device. Devices incorporating as an integral part, a substance which, if used separately, may be considered to be a medicinal product within the meaning of Directive 2001/83/EEC, and which is liable to act on the body with action ancillary to that of the device, fall within the scope of the Medical Devices Directive 93/42/EEC. Clinical investigation submissions of such devices should be made to the MHRA in the usual way.

3.7 Additional Considerations

3.7.1 Number of devices proposed for clinical investigation
In assessing risks to health or safety the MHRA will take into consideration the number of devices to be included within a clinical investigation. There must be a sufficient number in order to demonstrate performance satisfactorily and to reveal significant risks to patients’ health and safety. The number should not be so great however as to place at risk more patients than necessary at a time when 3rd party assessment of device-related risks has not been carried out. It is therefore important that the number reflects the aims of the investigation taking into account the perceived risk of the device and comply with relevant medical devices Standards where appropriate.

3.7.2 Clinical Investigation Duration
The duration of the clinical trial of a medical device should be sufficient to realistically test the device and allow identification of any associated risks. Longer term safety problems should be identified under Medical Devices Vigilance (MDV). The duration of the trial and follow-up must however be in line with relevant medical device Standards where appropriate.

3.7.3 Type of Investigation
The majority of clinical trials of medical devices will not include a control group. If control groups are necessary however, they should be randomised and prospective, except in exceptional circumstances.

3.7.4 End Points
The end point of the trial should be carefully selected to enable the results of the aims and objectives of the study to be determined under normal condition of use.

3.7.5 Labelling
It is essential that all devices intended to be used for clinical investigation must bear the words “exclusively for clinical investigation”. It is important to recognise that such wording may be confusing for clinical staff, in that it may be thought that the clinical investigation being referred to is that of a patient rather than the device. Manufacturers should therefore fully explain this to
investigators and ensure all staff coming into contact with the device understands. The device should be clearly segregated from any similar device that is in routine use. If the device has been CE marked for another purpose, explanatory labelling to this effect should be attached to the device under investigation.

3.7.6 Research Ethics Committee Opinions
For all studies that fall under the scope of the Medical Devices Regulations a relevant Research Ethics Committee (REC) opinion is required from the National Research Ethics Service (NRES) via the Integrated Research Application System (IRAS). This can be sought in parallel with the MHRA approval. If the REC approval has not been obtained at least 60 days before the intended clinical investigation, it should be forwarded to the MHRA as soon as it becomes available.

3.7.7 HRA Approval
HRA Approval is the new process for applying for approvals for all project-based research in the NHS led from England and replaces previous systems including the NIHR Coordinated System for gaining NHS Permission (CSP).

No clinical investigation of a medical device should be started until both REC and MHRA, HRA and Local Trust/R&D/Confirmation of Capacity and Capability/Joint Research Compliance Office approval have been received.

3.7.8 New Interventions Committee
For device studies occurring at Imperial College Healthcare NHS Trust, a copy of the protocol should be sent to the Trust New Interventions Committee for review prior to seeking ethics and regulatory approval:

Contact Details:
Dr Onn Min Kon
Email: onn.kon@imperial.ac.uk

3.8 MHRA Processing of Approval Application

3.8.1 Initial receipt of documentation
Following receipt of the required documentation, the MHRA send an acknowledgement letter to the manufacturer, a reference number (that should be quoted in all communications) and the starting date for the notification period.

If the documentation is incomplete, the manufacturer will be contacted as soon as possible to allow the missing information to be forwarded to the MHRA. The 60-day assessment clock starts from the date of the formal acknowledgement of receipt of the complete notice.

3.8.2 Expert Assessors
Copies of the application are then sent to one or more assessors who have expert knowledge of aspects of clinical investigation of devices. Assessors
from outside the Department of Health will have signed a statement of confidentiality incorporating a declaration of any conflict of interest. It is however possible at the time of submission, for manufacturers to name the institutions or individuals who they may not wish to act as assessors for the investigation in question.

3.8.3 Additional Information
Each expert assessor is allowed 14 days in which they will be able to request, through the MHRA, any further information that they think necessary in order for a proper assessment of the proposed clinical investigation to be made. Please supply any requested information as soon as possible, so that an adequate assessment of all relevant data can be completed. The 60 day clock does not stop while this information is being assembled.

3.8.4 MHRA Decision
If after considering all the information provided, the MHRA are satisfied that there are no grounds relating to health, safety or public policy whereby the proposed clinical investigation should not proceed, the MHRA will notify the applicant of this decision.

If the MHRA consider that the proposed 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.

The following may be considered as unjustifiable risks to public health:

i. where there are reasonable grounds to suspect that a device does not satisfy relevant Essential Requirements; or

ii. 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); or

iii. 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

iv. where there is inadequate/incomplete pre-clinical or animal data in order to make it reasonable for clinical testing to commence, or

v. where insufficient information has been submitted to enable a proper assessment of the safety aspects of the proposed clinical investigation to be made; or

vi. 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 UK Competent Authority to complete its assessment.

If the application raises grounds for objection, it is possible to re-submit revised documentation, so long as 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 completed PCA 1 and 2 forms via IRAS
should be provided. The reasons for the objection will remain confidential
between the MHRA, the expert assessors and the manufacturer. Any
further questions or issues raised by the MHRA will then only be in relation
to the information supplied to address the original grounds for objection. A
covering letter should therefore be provided with the original submission
stating that the documentation does not differ from that provided with the
original submission, except in those sections that address the original
grounds for objection.

It is advised that you 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.

3.9 Changes or Modifications to the Protocol
Any changes that are made to the protocol must be notified to the MHRA and not
implemented until a letter of agreement has been obtained from the MHRA. Any
requests for change or modification to the protocol should state the MHRA
reference number, proposed change, the reasons for the proposed change and a
statement by or on behalf of the manufacturer to the effect that such changes do
not increase the risk to either patient, user or third party.

The MHRA may request a new clinical investigation notification if the modification
to the protocol is thought to increase the risk to either the patient or the user, or if
the MHRA consider that the changes proposed constitute a new investigation.

3.10 Final Written Report
The MHRA must be notified when a clinical investigation comes to an end. The
MHRA may require a copy of the final written report of a clinical investigation of a
device falling within the scope of the Medical Devices Directive. In certain cases
such as where a serious adverse event has occurred associated with a CE-marked
device that was involved in a clinical investigation that the MHRA had approved, or
where a novel technology has been investigated, it is extremely likely that a final
report would be requested.

3.11 Adverse incidents involving devices undergoing clinical investigation
All serious adverse incidents must be reported to the MHRA, whether it is initially
thought to be device related or not. If adverse events arise out of the same
investigation being carried out in other EU countries they should also be reported to
the MHRA, as they may have a direct influence on the status of the UK
investigation. Such reports should 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 MHRA have the right to withdraw their approval, if it decides that the serious
adverse events give rise to issues of public health.

3.12 Humanitarian use of non-CE-marked devices
The MHRA may authorise the use of individual non-CE-marked devices falling
within the scope of the Medical Devices Regulations on humanitarian grounds,
provided that they are satisfied that such use would be in the best 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 approval only applies to the use of the individual device for a named individual within the UK. Failure to comply with these requirements constitutes a criminal offence. For full details of the humanitarian use of non-CE marked devices, together with the relevant forms may be found on the MHRA website https://www.gov.uk/guidance/exceptional-use-of-non-ce-marked-medical-devices

For further guidance on applying for MHRA approval, any queries regarding MHRA guidance or the clinical investigation procedure should be addressed to:

Devices.Regulatory@mhra.gov.uk

or:

Daniella Smolenska
Regulatory Affairs Manager (Medical Device Clinical Trials)
Floor 4 orange zone
151 Buckingham Palace Road
London
SW1W 9SZ
Tel: 020 3080 7363

4. REFERENCES

MHRA Guidance for Manufacturers on Clinical Investigations to be carried out in the UK

MHRA Information for Clinical Investigators

MHRA Guidance on the Biological Safety Assessment

MHRA conformity assessment

MHRA Medical Devices: Conformity and CE mark

Guidance document - Classification of Medical Devices - MEDDEV 2.4/1 rev.9

93/42/EEC Medical Devices Directive
EEC Active Implantable Medical Devices:
EEC Community Code relating to medicinal products for human use
https://ec.europa.eu/health/documents/eudralex/vol-1_en

5. **APPENDICES**

5.1 **Appendix 1: Guidance notes 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:

  i. The availability of suitable alternatives
  ii. The selection procedures and systems for sourcing the tissue/derivative
  iii. The details of the production processes and animals used
  iv. The source country including the assessment of geographical risk
  v. The nature of the starting materials
  vi. The systems for inactivation or removal of transmissible agents
  vii. The quantity of animal starting tissues or derivatives required to produce one unit of medical device
  viii. The tissues or derivatives of animal origin coming into contact with the patients and users, and the route of application
  ix. The 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.
5.2 Appendix 2: Guidance Notes on Clinical Investigations of Active Devices


The following information must be provided as part of the clinical investigation submission to support claims of compliance with the essential requirements of Medical Devices legislation.

5.2.1 General
i. Essential Requirements Checklist detailing how these requirements have been addressed, including references to harmonised standards as appropriate. NB: The application of harmonised standards is voluntary and it is acceptable to 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.

ii. 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.

iii. 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.

iv. 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.

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

5.2.2 Active Implants

ii. The results of animal studies.

iii. Performance statistics and adverse incident data of earlier model, when device is the next generation of an earlier design.
5.2.3 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 is used by MHRA as a framework 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 = 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.
5.3 Appendix 3: Guidance notes on Medical Devices incorporating a medicinal substance or human blood derivative having ancillary action

The following information should be provided with regard to the medicinal substance and/or the human blood derivative:

i. Intended purpose within the context of the device and the risk analysis.
ii. Source, product licence (where applicable), quantity/ dosage of the medicinal component, and the method by which the substance is incorporated into the device.
iii. Method of manufacture (solvents/reagents used in processing, residuals).
iv. 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.

v. Qualitative and quantitative tests carried out on the medicinal substance.
vi. Stability data in relation to the expected shelf-life/ lifetime of the device.

vii. Toxicicological profile (summary of results of toxicity testing / biological compatibility).
   - This should include the effect on reproductivity, embryo/foetal and perinatal toxicity and the mutagenic / carcinogenic potential of the medicinal substance.

viii. Pharmacodynamics of the medicinal substance in relation to the device.

ix. Pharmokinetic 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.

x. Local tolerance (particularly where the route of exposure is different to the conventional application)

xi. Clinical documentation (clinical data demonstrating the usefulness of the medicinal substance)

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

xii. Control of the starting materials

xiii. - control of plasma source e.g. summary of the European Plasma Master File,

xiv. - production of the blood derivative

xv. - Manufacturers may wish to cross-reference a granted Clinical Trial Authorisation (CTA) or marketing authorisation for a medicinal product.

xvi. - Pharmacodynamics of the medicinal substance in relation to the device.
5.4 Appendix 4 - Medical devices: conformity assessment and the CE mark

A notified body is an organisation that has been designated by an EU member state (the designating authority) to assess whether manufacturers and their medical devices meet the requirements set out in legislation. The Medicines and Healthcare products Regulatory Agency (MHRA) is the designating and competent authority in the UK. Manufacturers can apply to any notified body in the EU and once they have the necessary certification their products can be sold anywhere in the EU. Following an appropriate assessment, the notified body will issue relevant certification allowing manufacturers to put CE-marks on their products and put them on the market in the EU.

5.4.1 Role of the notified body

A notified body’s tasks will vary depending on the classification of the products concerned and the conformity assessment route a manufacturer has chosen. The conformity assessment procedures can be found in the annexes of each of the 3 pieces of legislation.

Typical activities that can be undertaken by a notified body include:

- full quality assurance: the notified body will carry out an assessment of the manufacturer’s quality system, including design; they will sample across the range of products and processes to ensure that the requirements are being met
- examination of the design: the notified body will assess the full design dossier relating to each type of product to ensure that they meet the requirements
- type examination: the notified body will assess the full technical information relating to each type of product and carry out appropriate testing of a representative sample of production to ensure that it meets the requirements
- verification: the notified body will either test every unit or every batch of product to ensure that they are meeting the requirements before the manufacturer can place them onto the market
- production and product quality assurance: the notified body will carry out an assessment of either the manufacturer’s quality system covering production and inspection (production QA) or final inspection (product QA); they will sample across the range of products to ensure that relevant technical files are available as well as ensuring that the relevant processes being undertaken meet the requirements
- conduct unannounced audits of manufacturers - it’s now mandatory for notified bodies to conduct unannounced audits of manufacturers according to Annex III of the Commission Recommendation (2013/473/EU) of 24 September 2013

5.4.2 Assessment routes

A CE mark can be placed on a product to show that the medical device has met the requirements when it has passed the conformity assessment. Further guidance on: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/476902/Conformity_assessment_routes_chart_Nov15.pdf

i. Class I devices

If the manufacturer is satisfied that the medical device complies with the requirements in the MDD, must write a statement to declare this. Will then need to apply to a notified body (see: https://www.gov.uk/government/publications/notified-bodies-for-medical-devices) to
approve and certify the parts of the manufacturing process that relates to sterility or metrology, if the medical device includes sterile products or a measuring function.

See guidance on Class I medical devices:
https://www.gov.uk/government/collections/guidance-on-class-1-medical-devices

The product must then be registered (refer to: https://www.gov.uk/guidance/register-as-a-manufacturer-to-sell-medical-devices) with the relevant competent authority. This is the MHRA in the UK.

The CE mark can be placed on the product and go on the market when this process is complete.

ii. Class IIa devices
The device will need to have a declaration of conformity with the requirements in the MDD as well as the Medical Devices Regulations 2002. An application should be submitted to a notified body to carry out a conformity assessment to approve the declaration.

The type of assessment can be either an:

- examination and testing of each product or homogenous batch of products (Annex IV of the MDD)
- audit of the production quality assurance system (Annex V of the MDD)
- audit of final inspection and testing (Annex VI of the MDD)
- audit of the full quality assurance system (Annex II of the MDD)

A CE mark can be placed on the product and this can be placed on the market upon receipt of a certificate from the notified body.

iii. Class IIb devices
If the device falls into this category then either the following must be carried out:

- an annex II audit of full quality assurance system or;
- an annex III type-examination plus either option 1, 2 or 3 given for the class IIa devices above

A CE mark can be placed on the product and this can be placed on the market upon receipt of a certificate from the notified body.

iv. Class III devices
If the device falls into this category then either the following must be carried out:

- an annex II audit of the full quality assurance system including a design dossier examination or;
- an annex III type-examination plus 1 of the option 1, 2 or 3 given for the class IIa devices above

A CE mark can be placed on the product and this can be placed on the market upon receipt of a certificate from the notified body.