Queen's University Belfast

Research and Enterprise

Standard Operating Procedure
Research Governance

Title:	**Clinical Investigations of Medical Devices**		
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	Name and Position	Signature	Date
Author:	Mrs Louise Dunlop Head of Research Governance		29-03-2017
Reviewed by:	Professor James McElnay, Chair Research Governance and Integrity Committee		22-03-2017
Approved by:	Mr Scott Rutherford Director, Research and Enterprise		15.3.2017

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Revision Log

* For all University sponsored research seeking approval for the clinical investigation of a medical device

Previous Version number	Date of Review/Modification	Reason for Review/Modification	New Version Number
Final v 1.0	10/11/09	Annual Review	Final v 1.0
Final v 1.0	19/08/11	Annual Review/ Update following MHRA GCP Inspection	Final v 2.0
Final v 3.0	21/08/12	Periodic Review	Final v 4.0
Final v 4.0	06/10/2014	Periodic Review	Final v 5.0
Final v 5.0	01/12/2016	Periodic Review	Final v 6.0

1. Purpose

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

2. Introduction

The Medical Devices Regulations 2002 (SI No 618), as amended by the Medical Devices (Amendment) Regulations 2008, came into force on 13 June 2002 and implement the provisions of the Medical Devices Directive 93/42/EEC (as amended by Directive 2007/47/EC), the Active Implantable Medical Devices Directive 90/385/EEC (as amended by Directive 2007/47/EC) and the In Vitro Diagnostic Medical Devices Directive 98/79/EEC. These Regulations establish systems under which a manufacturer must submit to the UK Competent Authority, information about clinical investigations of medical devices to be carried out in the UK.

The regulatory framework for the development of medical devices is due to change with the Medical Device Directives being replaced by a Regulation in early 2017. A transition period will apply when both current and new regulatory expectations operate in parallel.

An exemption currently exists to allow a non-CE marked medical device or a CE marked device for a new purpose to be used in on a compassionate use basis. This use is permitted only after review of the case by the MHRA and is granted for an individual named-patient. This exemption cannot be used to gather clinical evidence for the approval of a medical device.

The Competent Authority in the UK is the Medicines and Healthcare products Regulatory Agency (MHRA).

Manufacturers wishing to make an application for pre-clinical assessment of a proposed clinical investigation 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. The controls are intended to ensure the safety and performance of medical devices and to prohibit the marketing of devices which might compromise the health and safety of patients, users or any relevant third party (where appropriate).

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

- A compilation of the relevant scientific literature currently available on the intended purpose of the device and the techniques employed, together with, if appropriate, a written report containing a critical evaluation of the compilation; or
- The results and conclusions of a specifically designed clinical investigation.

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 representative in the European Union) must give 60 days prior notice to the Secretary of State for Health by writing to the MHRA. If, within 60 days of formal acceptance of the Notice, the UK Competent Authority has not given written notice of the objection, the clinical investigation may proceed. The MHRA may object on grounds relating to public health or public policy.

3. Scope

This SOP applies to all studies where the University is acting in the capacity of Sponsor, or Co-Sponsor. It applies to all members of University staff; both academic and support staff as defined by Statute 1, including honorary staff and students.

4. Responsibilities

4.1 Chief Investigator

To establish whether or not regulatory approval is required for their Clinical Investigation and to ensure that this is in place prior to the commencement of a trial. Where there is any doubt the CI must contact the MHRA and obtain written confirmation of their advice. Should the scope of the planned research change since contacting the MHRA further advice should be sought. The CI is ultimately responsible for the accuracy and timely provision of information to the MHRA.

The CI must ensure that the study is logged onto the Human Subjects Database and that the correct level of risk is designated to the proposed research. The risk levels are detailed in the below table:

Risk	Descriptor
Level 1	Those projects which although involving human subjects are in no way associated with a medicinal purpose or do not involve issues such as alcohol and illicit drug use or higher risk sexual behaviour. Level 1 projects essentially involve research into, for example, behaviour, attitudes, rights and education issues. These projects do not include an intervention[1].
Level 2	Those projects that have more relevance to healthcare and include, for example, survey work on access to health care or issues, such as alcohol and illicit drug use or higher risk sexual behaviour. These projects do not include an intervention[1].
Level 3	These projects essentially involve research involving collecting data (including risk factor data) in human subjects and correlating this with, for example, health status, and advances in diagnostics. The projects do not involve altering treatment regimens or the standard of routine care that these individuals receive. These projects do not include an intervention[1].
Level 4	These studies generally either involve an intervention which has the aim of changing health status or behaviour or involve procedures that are generally more invasive in nature, but do not have the attributes/characteristics of Level 4b studies.
Level 4b	These studies involve Clinical trials of Investigational Medicinal Products or clinical trials into medical devices or involve procedures which aim to induce illness or other conditions (eg inflammation) in study subjects for the purpose of testing the efficacy of new treatment approaches.

[1]An intervention is classed as a change directly related to the study that may alter the research subject's health, physically or mentally and includes any potential to alter behaviour as a result of participation.

The Human Subject Database will be audited by the Universities Insurance provider annually and any discrepancies will be reported back. No indemnity will be in place for any study that has not been logged onto this database.

4.2 Sponsor

To ensure that the appropriate regulatory approval is in place.

5. Procedure

5.1 Is a clinical investigation required?

The manufacturer of the medical device needs to determine whether a clinical investigation is required:

- What are the Essential Requirements relevant to the device in question with which compliance must be demonstrated?
- What data is required in order to demonstrate this compliance?
- What testing is necessary to produce this data e.g. bench testing, animal testing?
- Is clinical data required to demonstrate compliance?
- If so, does this clinical data already exist on the device in question?

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

- The introduction of a completely new concept of device into clinical practice where components, features and/or methods of action, are previously unknown;
- Where an existing device is modified in such a way that it contains a novel feature particularly if such a feature has an important physiological effect; or where the modification might significantly affect the clinical performance and/or safety of the device;
- Where a device incorporates materials previously untested in humans, coming into contact with the human body or where existing materials are applied to a new location in the human body 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.

5.2 Making an application for pre-clinical assessment

5.2.1 Prior to making a notification

Prior to submitting a notification to the MHRA, 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. A significant percentage of the grounds for objection that have been raised have resulted from the failure to supply the necessary data within the 60 day time period allowed by the regulations.

5.2.2 How to apply

Application for assessment of a proposed clinical investigation of a medical device is made by completing forms PCA1 and PCA2 and attaching the information

requested on the forms. Guidance is available from the MHRA website https://www.gov.uk/topic/medicines-medical-devices-blood/medical-devices-regulation-safetyand the PCA1 and PCA2 forms have been incorporated into the Integrated Research Application Systems (IRAS) and can be completed online at http://www.myresearchproject.org.uk.

All documentation should be clearly labelled "documentation only" and sent by recorded delivery.

A total of eight copies for each full submission is required and must be presented with all pages in their correct numbered sequence, including reprints, diagrams, tables and other data. The method of reproduction must allow for legible presentation of the text and any relevant drawings and their captions.

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.

5.3 Supporting Documentation

All applications must contain a signed statement:

- *"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;
- Whether or not the device incorporates, as an integral part, a substance of human blood derivative referred to in Section 7.4 of Annex 1 of the Medical Devices Directive and Section 10 of the Active Implantable Medical Devices Directive;
- Whether or not the device is manufactured utilising tissues of animal origin as referred to in Directive 2003/32/EC.

In addition, the following information should be provided:

5.3.1 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 EC;
- *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.

5.3.2 Details allowing device to be identified

- Generic name of device;
- Model name;
- Model number(s), if any;
- Name and Address of Manufacturer.

5.3.3 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 operations 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).
- A description of the methods of manufacturer, in particular as regards sterilization and identification of packaging used for sterilisation of device.
- *Identification of any tissues of animal origin as referred to in Directive 2003/32/EC 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; and any other risk management measures that have been applied to reduce the risk of infection;
- *Identification of any special manufacturing conditions required and if so how such requirements have been met;
- *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 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.

* Denotes additional information that may be requested by the MHRA.

5.4 Clinical Investigation Plan

A copy of the Clinical Investigation Plan and Investigator's Brochure must be provided, which should include the following information:

5.4.1 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;
- Copy of informed consent;
- Reference to important relevant scientific literature (if any) with an analysis and bibliography;
- Confirmation of insurance of subjects;
- Copy of Participants Information Sheet.

5.4.2 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.

5.4.3 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.

5.5 Documentation to be kept available

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 with the notification but should in all cases be available for the MHRA on request:

- 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 contract, 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;
- 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 Guidance Document No 5: Guidance on Biocompatibility Assessment, available from the Competent Authority/MHRA;
- Details of the method(s) of sterilisation. If the chosen sterilisation process is by the use of moist heat (steam) then 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.
  - i Specification of manufacturing environment used;
  - ii Details of any cleaning process prior to sterilisation;
  - iii Method of sterilisation;
  - iv Parameters of the sterilisation process;
  - v Site(s) of sterilisation (if different from manufacturing site(s);
  - vi Packaging materials used;
  - vii Summary of sterilisation validation data;
  - viii Details of routine monitoring of the sterilisation process.
- Documentation demonstrating compliance of the device with the Essential Requirements with regard to electrical safety;

- 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.

5.6 Special features of clinical investigations

5.6.1 Proposed number of devices

In assessing risks to health and safety, one of the areas that will be 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. Therefore, the number 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.

5.6.2 Clinical investigation duration

The duration of a clinical investigation of a medical device should be sufficient to demonstrate the performance of the device over a period of time, and allow for the identification and risk assessment of any associated unacceptable adverse incidents during that period. The duration of a clinical investigation and follow up period must be in line with relevant medical device Standards, where appropriate.

5.6.3 Post Market Clinical Follow-up

The Medical Devices Directive and Active Implantable Medical Devices Directive 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.

5.6.4 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 will depend on the aims of the investigation. However, if they are deemed necessary control groups should be randomised and prospective, except in exceptional and justifiable circumstances.

5.6.5 End Points

The chosen endpoints should support the stated aims and objectives of the clinical investigation under normal conditions of use.

5.6.6 Labelling

All devices intended for clinical investigation must bear the wording "exclusively for clinical investigation". It is important to ensure that all staff using or coming into contact with the device understand the meaning of this wording. In addition, the device being investigated should be segregated, where possible. 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.

5.7 Fees

A charge will be made by the MHRA to the manufacturer for the assessment of the proposed clinical investigation, depending on whether the device is categorised as Group A (low risk) or Group B (high risk). The current fees can be obtained from the MHRA website (last accessed October 2014):
http://www.mhra.gov.uk/Howweregulate/Devices/Clinicaltrials/index.htm

5.8 Where do I apply to?

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

Mrs Daniella Smolenska
Regulatory Affairs Manager (Medical Devices and Clinical Trials)
Medicines and Healthcare products Regulatory Agency (MHRA)
5 Magenta
151 Buckingham Palace Road
London, SW1W 9SZ
Tel: 020 30806000
Email: Daniella.Smolenska@mhra.gsi.gov.uk

5.9 Next Steps

5.9.1 Research Ethics Committee Opinions

For all clinical investigations of devices falling within the scope of the Medical Devices Regulations, a relevant Research Ethics Committee (REC) opinion is required. This opinion may be obtained in parallel with the MHRA. 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.

Further information can be obtained from SOP QUB-ADRE-003.

5.9.2 How the MHRA will process your application

On receipt of your application, the MHRA will process it as outlined in Appendix 3. The MHRA will then acknowledge receipt of notice to the manufacturer. Within this letter there will be a reference number that should be quoted on all communication to the MHRA and a starting date for the notification period.

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 60 day assessment clock will start from the date of the formal acknowledgement of receipt of the complete notice.

Copies of the clinical investigation documentation will be sent to at least one assessor with knowledge of medical devices. These assessors, from outside of the MHRA, will have signed a statement of confidentiality incorporating a declaration of any conflict(s) of interest. However, in the interests of confidentiality manufacturers may, at the time of the original submission, name the institutions/individuals whom they may not wish to act as assessors. Any documentation released to assessors must be returned to the MHRA and no copies retained.

Each expert assessor will be allowed 14 days in which he/she will be able to request, through the MHRA, any further information deemed necessary in order to make a proper assessment. The 60 day clock will not stop whilst this requested information is being assembled.

5.9.3 MHRA Decision

If, after consideration of all the evidence provided, the MHRA considers that there are no grounds relating to health or safety or public policy for the clinical investigation to proceed, the MHRA will notify the applicant of this decision.

In the event that the MHRA considers there to be the possibility of unjustifiable risks (as outlined in appendix 4) to public health or safety, the MHRA will notify the applicant of their objection to commencement of the proposed clinical investigation.

If the MHRA raises grounds for objection, it will notify other EU Competent Authorities and the European Commission of their decision and the grounds for that decision. 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.

The applicant may re-submit revised documentation, provided the reason for refusal has been addressed. An appropriate fee will need to accompany the subsequent notice. 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 MHRA's original concerns.

5.10 Request for amendment.

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 amendment should include:

- The MHRA reference number;
- The proposed change(s) to the clinical investigation/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.

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 the amendment to constitute a new investigation.

5.11 Final Written Report

Manufacturers are required to notify the MHRA when a clinical investigation comes to an end. 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. 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.

5.12 Early Termination of Clinical Investigation

Manufacturers are required to notify the MHRA of the early termination of a clinical investigation and provide a justification for the early termination. 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.

5.13 Adverse Incidents

All serious adverse incidents must be reported to the MHRA, even those that occur outside the UK for the same investigation. These reports should not be delayed while the manufacturer attempts to gain access to, or test, the device or make a full investigation. There are a number of different forms in use, depending on the medical device in question. Please refer to

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.

6. References

MHRA. EU Medical Devices Directives. Guidance for manufacturers on clinical investigations to be carried out in the UK. June 2008 Updated August 2011.
http://www.mhra.gov.uk/home/groups/es-era/documents/publication/con007504.pdf
(last accessed January 2017)

7. Appendices

Appendix 1	Guidance notes on medical devices incorporating tissue of animal origins.
Appendix 2	Details of medicinal substances acting ancillary to the medical device.
Appendix 3	MHRA process.
Appendix 4	List of unjustifiable risks as outlined in MHRA guidance document.

Guidance notes on medical devices incorporating tissues of animal origins

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 derivates, 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.

GUIDANCE NOTES 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)

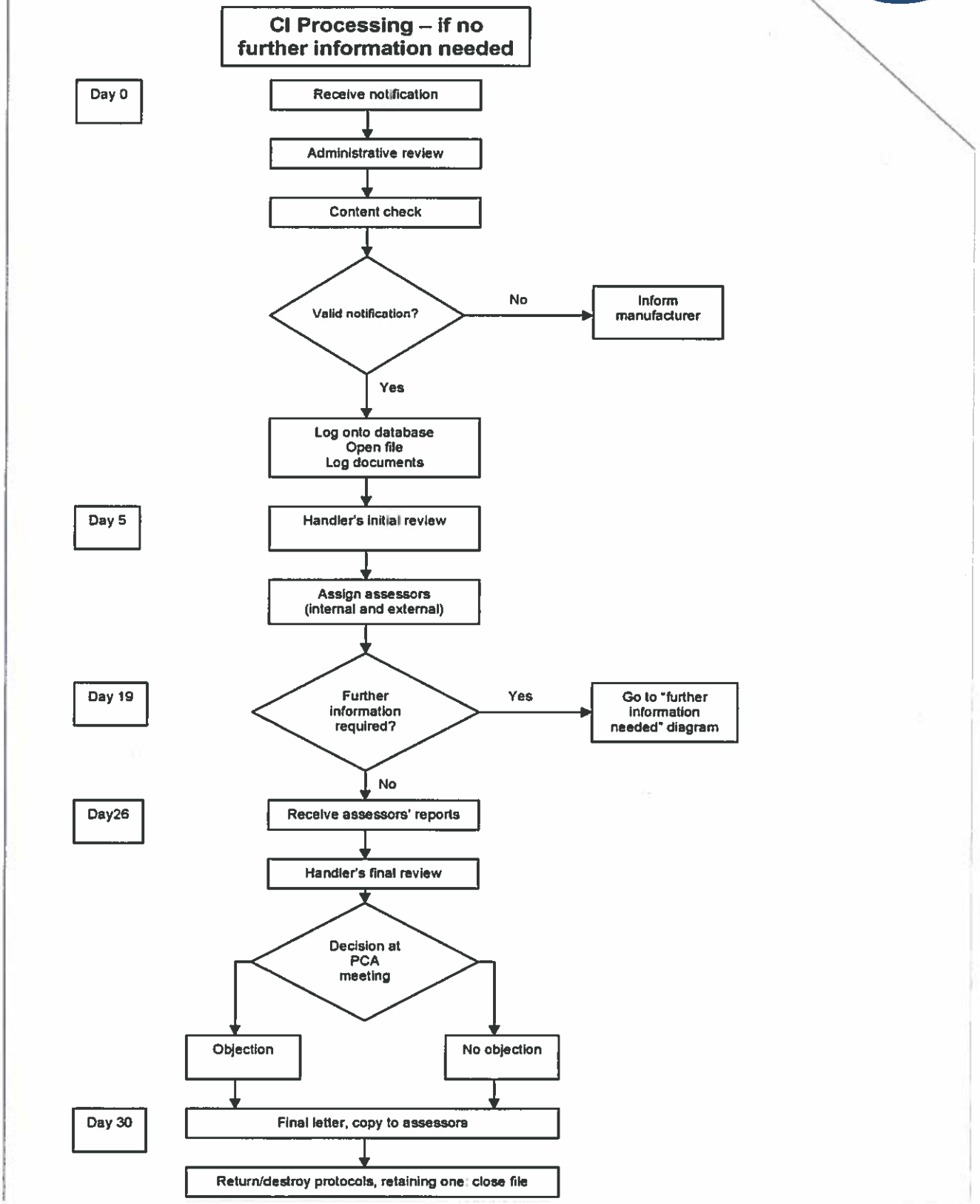
Additional information required with regard to the medicinal substance only;

- 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/foetal and perinatal toxicity and the mutagenic / carcinogenic potential of the medicinal substance.
- Pharmacodynamices of the medicinal substance in relation to the device.
- 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.
- 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;
- Pharmacodynamices of the medicinal substance in relation to the device.

"Guidance for manufacturers on Clinical Investigations to be carried out in the UK"

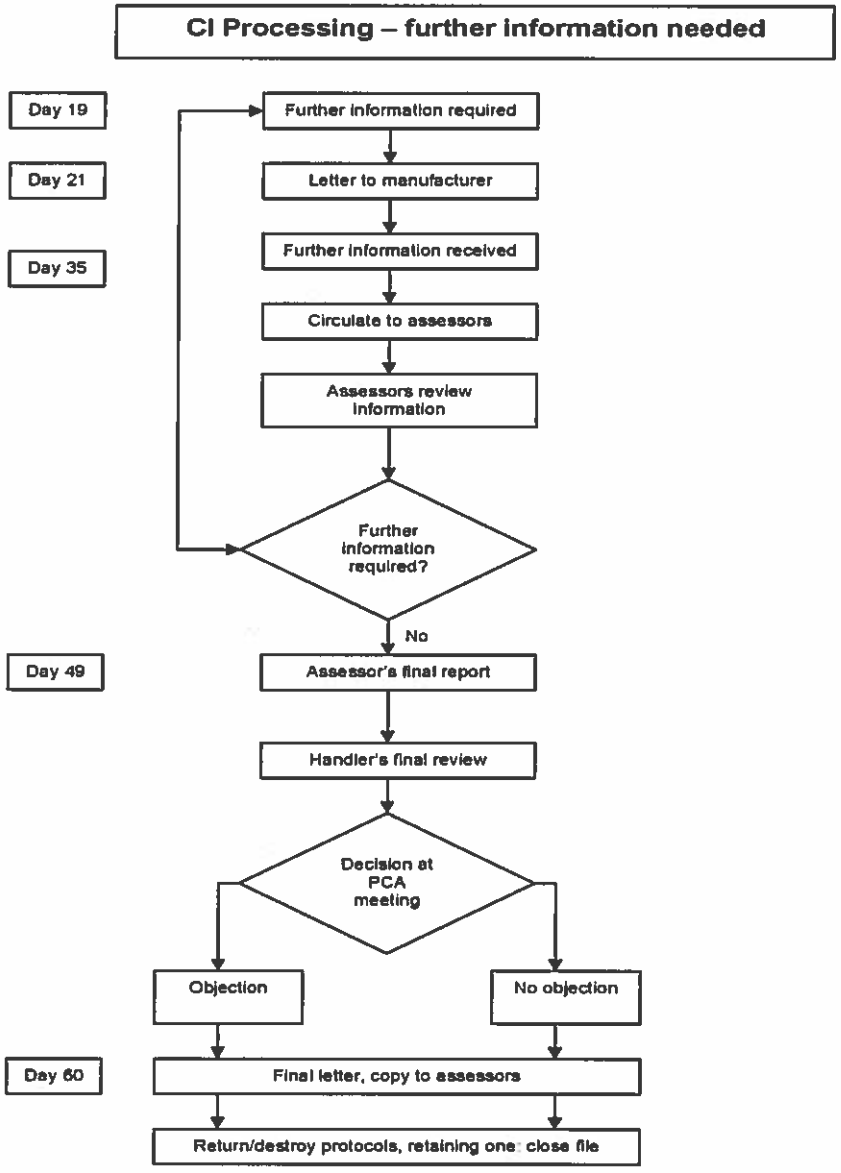
ANNEX 1

FLOW DIAGRAM OF CLINICAL INVESTIGATION PROCESSING



ANNEX 1

FLOW DIAGRAM OF CLINICAL INVESTIGATION PROCESSING



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

- Where there are reasonable grounds to suspect that 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 (IS 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 of 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 sufficient 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 UK Competent Authority to complete its assessment.