Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Guidance on legislation

Clinical investigations of medical devices – guidance for manufacturers

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

Revision history

This version	Date published	Changes
V1.0	October 2013	n/a
V2.0	March 2016	Revised appendix 4 – software and programmable devices
V3.0	July 2017	Revised sections ‘How to apply’ and ‘MHRA Decision’ to reflect current requirements. Plus, other minor changes.
V3.1	September 2018	Revised MHRA contact information and form name change
V4.0	January 2019	Revised sections on REC opinion and HRA approval. Removal of sections concerning making an application and documentation requirements, and Appendixes 2-5.
V5.0	January 2020	Revised section ‘Is a clinical investigation required: the practical decisions’
V6.0	January 2021	Revised for UK regulations
V7.0	May 2021	Revised for Northern Ireland

V8.0	March 2024	Clarifications to when equivalence can be used vs when a clinical investigation is required
V9.0	April 2024	Revised MHRA contact information and links to other guidance
V10.0	April 2025	Clarification of term used in validation and their regulatory basis Updates to reflect ‘participants’ as preferred terminology Minor clarifications for readability

Clinical investigation in the UK:

It is important to note that the rules for notifying the MHRA of a clinical investigation in Great Britain (England, Wales and Scotland) differ from those applicable to Northern Ireland.

The Northern Ireland Protocol requires Northern Ireland to continue to align with EU rules for devices after 1 January 2021. Therefore, the Medical Device Regulation (EU) 2017/745 (MDR) and the In Vitro Diagnostic Medical Device Regulation (EU) 2017/746 (IVDR) will apply in Northern Ireland from 26 May 2021, and 26 May 2022 respectively, in line with the EU's implementation timeline.

This means that clinical investigations being conducted in Northern Ireland must meet the requirements of the EU MDR and be submitted to MHRA in accordance with these regulations.

Clinical investigations being conducted in Great Britain need to meet the requirements of the UK MDR 2002.

Where a clinical investigation includes sites in **both** Great Britain and Northern Ireland, submission to the MHRA must be made in line with the requirements of the EU MDR. By meeting the EU MDR, requirements of the UK MDR 2002 for clinical investigations are deemed to be satisfied. Therefore, a single application made to MHRA under the EU MDR will cover any sites proposed in both Great Britain and Northern Ireland for the same clinical investigation.

This guidance document applies to all clinical investigations being conducted in the UK; however, text boxes highlight where requirements differ for Northern Ireland.

1. Unless an exemption applies, all medical devices to be used on humans must be UKCA/CE marked for the purpose that they are being used for, unless they are being used as part of a clinical investigation designed to investigate the performance and safety of the medical device or accessory.

2. In order to be able to UKCA/CE mark any device, a manufacturer must demonstrate that the stated device complies with the relevant essential requirements as listed in Part II and Part III of the UK Medical Devices Regulations 2002 (UK MDR 2002), Annex I (as modified by Schedule 2A to the UK MDR 2002) or the general safety and performance requirements (GSPRs) in Annex I of the EU MDR.

   To demonstrate such compliance, it will usually be necessary to provide clinical data, which can consist of:

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

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

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

4. When UKCA/CE marking a device, unless safety and performance can be adequately demonstrated by other means, data generated from a specifically designed clinical investigation of a medical device are likely to be required, in particular with implantable and class III devices. Such an investigation must be designed to:

    - verify that under normal conditions of use the performance characteristics of the device are those intended by the manufacturer; and
    - determine any undesirable side effects under normal conditions of use and assess whether these constitute risks when weighed against the intended performance of the device.

Northern Ireland

With the case of implantable and class III devices, clinical investigations shall be conducted unless:

- The device is an iterative modification of a device already on the market by the same manufacturer; and
- The modified device is equivalent to the marketed device; and
- The clinical evaluation of the marketed device is sufficient to demonstrate conformity of the modified device with the GSPR.

Where the manufacturer of the modified device is not the manufacturer of the marketed device, then in addition to the above bullet points the following must also be in place:

- The two manufacturers must have a contract in place that allows the manufacturer of the modified device full access to the technical documentation of the marketed device on an ongoing basis; and
- The original clinical evaluation for the marketed device has been performed in compliance with Regulation 2017/745.

Clinical investigations are also not required for implantable and class III devices that:

- Where placed on the market or put into service before 26th May 2021 in accordance with Directive 90/385/EEC or Directive 93/42/EEC; and
- The clinical evaluation is based on sufficient clinical data and complies with relevant product-specific common specification where available.

OR

- Are sutures, staples, dental fillings, dental braces, tooth crowns, screws, wedges, plates, wires, pins, clips or connectors; and
- The clinical evaluation is based on sufficient clinical data and complies with relevant product-specific common specification where available.

Clinical investigations must be designed to:

- establish and verify that, under normal conditions of use, a device is designed, manufactured and packaged in such a way that it is suitable for one or more of the specific purposes listed in point (1) of Article 2 [of the regulation], and achieves the performance intended as specified by its manufacturer;
- establish and verify the clinical benefits of a device as specified by its manufacturer; and
- establish and verify the clinical safety of the device and to determine any undesirable side-effects, under normal conditions of use of the device, and assess whether they constitute acceptable risks when weighed against the benefits to be achieved by the device.

5. If you plan on using a non-UKCA/CE marked medical device on human participants you will be required to notify the MHRA of your planned clinical investigation**.**

6. A clinical investigation of a non-UKCA/CE marked device must be designed to establish that the performance claimed by the manufacturer can be adequately demonstrated, and that the device is judged to be safe to use on patients taking into account any risks associated with the use of the device when weighed against the expected benefits.

7. If the purpose of a proposed clinical investigation is other than as outlined above e.g. user handling or preference studies, it should not be carried out on a non-UKCA/CE marked device. Such studies should only be performed on UKCA/CE marked devices unless they form part of a study to investigate safety and performance for UKCA/CE marking purposes.

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

9. Before devices intended for clinical investigation in Great Britain are made available to a medical practitioner for the purposes of clinical investigation, the manufacturer or UK Responsible Person of the device must give 60 days of prior notice to the Secretary of State for Health by writing to the MHRA. All notifications should be submitted using the application process on the IRAS portal. If, within 60 days of formal acceptance of the Notice, the MHRA has not given written notice of objection, the clinical investigation may proceed. The MHRA may give such notice of objection on grounds relating to public health or public policy (UK MDR 2002: Regulations 16(4) and 29(3)).

Northern Ireland

Before devices intended for clinical investigation in Northern Ireland are made available to a medical practitioner for the purposes of clinical investigation, the sponsor of the clinical investigation (or their legal representatives in the European Union) must give 45 days of prior notice to the Secretary of State for Health by writing to the UK competent authority (the MHRA). MHRA will review the clinical investigation during the 45 days and will issue you with a final decision of either authorisation or refusal. The clinical investigation may not be conducted without authorisation by MHRA.

The MHRA may refuse authorisation if the clinical investigation does not meet the requirements of the regulation, the application is incomplete, the device or the Clinical Investigation Plan and Investigators Brochure do not correspond to state of scientific knowledge and do not provide evidence for safety, performance or benefit of the device (Regulation 2017/745 Article 71.4).

MHRA may extend the 45-day review period by a further 20 days should an external assessor be required to review the application. Sponsors will be made aware of this extension by email.

10. The legal requirements as to methodology and ethical considerations relating to clinical investigations conducted in Great Britain are set out in regulations 16 and 29 of the UK MDR 2002 and Part II, Annexes VIII and X (medical devices) and Part III, Annexes 6 and 7 (active implantable devices) of the UK MDR 2002 (as modified by Part II of Schedule 2A to the UK MDR 2002).

In particular the clinical investigation must:

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

Northern Ireland

1. The legal requirements as to methodology and ethical considerations relating to clinical investigations are set out in EU MDR (Chapter VI – *Clinical Evaluation and Clinical Investigations*, specifically Articles 62 – 82).

In particular the clinical investigation must:

- be designed and conducted in such a way that the rights, safety, dignity and well-being of the subjects participating in a clinical investigation are protected and prevail over all other interests and the clinical data generated are scientifically valid, reliable and robust;
- Ensure vulnerable populations and subjects are appropriately protected in accordance with Articles 64 to 68 of the regulation;
- Ensure the anticipated benefits to the subjects or to public health justify the foreseeable risks and inconveniences and compliance with this condition is constantly monitored;
- ensure the subject or, where the subject is not able to give informed consent, his or her legally designated representative has given informed consent in accordance with Article 63;
- ensure the subject or, where the subject is not able to give informed consent, his or her legally designated representative, has been provided with the contact details of an entity where further information can be received in case of need;
- ensure the rights of the subject to physical and mental integrity, to privacy and to the protection of the data concerning him or her in accordance with Directive 95/46/EC are safeguarded;
- be designed to involve as little pain, discomfort, fear and any other foreseeable risk as possible for the subjects, and both the risk threshold and the degree of distress are specifically defined in the clinical investigation plan and constantly monitored;
- ensure the medical care provided to the subjects is the responsibility of an appropriately qualified medical doctor or, where appropriate, a qualified dental practitioner or any other person qualified to provide the relevant patient care under clinical investigation conditions;
- ensure no undue influence, including that of a financial nature, is exerted on the subject, or, where applicable, on his or her legally designated representatives, to participate in the clinical investigation;
- involve only investigational devices that conform to the applicable general safety and performance requirements apart from the aspects covered by the clinical investigation and that, with regard to those aspects, every precaution has been taken to protect the health and safety of the subjects. This includes, where appropriate, technical and biological safety testing and pre-clinical evaluation, as well as provisions in the field of occupational safety and accident prevention, taking into consideration the state of the art;
- ensure that any subject, or, where the subject is not able to give informed consent, his or her legally designated representative, may, without any resulting detriment and without having to provide any justification, withdraw from the clinical investigation at any time by revoking his or her informed consent;
- Ensure the investigator qualifies for the role of investigator by having the necessary scientific knowledge and experience in patient care. Other personnel involved in conducting a clinical investigation shall be suitably qualified, by education, training or experience in the relevant medical field and in clinical research methodology, to perform their tasks;
- Be conducted at facilities that are suitable for the clinical investigation and shall be similar to the facilities where the device is intended to be used.

11. In addition, the principles of clinical investigations of medical devices are set out in the standard BS EN ISO 14155:2020 Clinical investigation of medical devices for human participants - Good clinical practice. *Please note, this is not a designated standard, however, we would expect manufacturers to adhere to this ISO standard as it is deemed to be best practice.*

Is a clinical investigation required: the practical decisions

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

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

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

- the device is an implantable or Class III medical device
- the introduction of a completely new concept of device into clinical practice where components, features and/or methods of action, are previously unknown
- where an existing device is modified in such a way that it contains a novel feature particularly if such a feature has an important physiological effect; or where the modification might significantly affect the clinical performance and/or safety of the device
- where a device incorporates materials previously untested in humans, coming into contact with the human body or where existing materials are applied to a new location in the human body or where the materials are to be used for a significantly longer time than previously, in which case compatibility and biological safety will need to be considered
- where a device, either UKCA/CE marked or non-UKCA/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.

14. Clinical Investigation notification to the MHRA will not be required if the medical device to be used is UKCA/CE marked for the purpose under investigation. However a notification may be required if the study will be conducted in Northern Ireland and involves additional procedures that are invasive and burdensome (see paragraph 25 for further details).

Clinical investigations: special circumstances

15. Change in the intended use/performance claims of a device

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

16. Comparative studies

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

17. Prototype devices

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

18. Clinical investigations also submitted to the FDA or other regulatory authorities

Manufacturers should clearly indicate whether the UK and non-UK protocols are the same. If not, the areas of difference should be referenced and an explanation of the reasons for the differences provided. It is recognised that the objectives of a clinical investigation which is also being carried out in a country or countries outside the UK, may be wider than those required by the UK MDR 2002/EU MDR. Changes to protocol requested by other regulatory authorities should be copied to the MHRA for information. At such times, manufacturers should indicate whether the changes instigated by the non-UK regulatory authority will also be made to the UK protocol.

19. In-house manufactured medical devices

Products manufactured in-house in a healthcare establishment and undergoing testing for proof of concept are not subject of the provisions of the UK MDR 2002 provided that the device is being manufactured and used on patients within the sole legal entity. In circumstances where the in-house manufacturer sees and intends a commercial medical application in the results generated (irrespective of whether the manufacturer and participants are part of the same legal entity) the manufacturer will need to notify the MHRA of a proposed clinical investigation.

See the common scenarios for healthcare establishments for further information and if there is any doubt as to the interpretation, contact the MHRA for clarification.

20. 'Off-label' use

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

21. Research tools

It is MHRA's general opinion that a device being used on humans for research purposes, where there is no intended medical purpose for the device, could be a research tool. However if a manufacturer sees and intends a medical application in the results generated from testing a device, then the device is no longer a research tool, but falls within the definition of a medical device.

Whether the regulations apply to a device will depend on the intended purpose foreseen by the device manufacturer.

If a proposed clinical study includes investigating use of a device for a medical purpose, then such a study is likely to fall within the remit of the UK MDR 2002/EU MDR and require notification to MHRA as a clinical investigation.

MHRA strongly recommend that manufacturers contact us for guidance on whether the regulations will apply before undertaking a study of this nature. When contacting MHRA please provide details of:

- Who has manufactured the device
- Who is conducting the proposed study
- What the intended purpose of the device is
- What the intended purpose of the proposed study is
- Whether any medical application is foreseen for the device
- Please provide a copy of the study protocol where possible

22. Humanitarian use of non-UKCA/CE UKNI/CE marked devices

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

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

Clinical investigations – things to consider

23. Number of devices proposed for clinical investigation

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

24. Clinical investigation duration

The duration of a clinical investigation of a medical device should be such as to permit the demonstration of performance over a period of time sufficient to represent a realistic test of the device, and allow identification and risk assessment of any associated unacceptable adverse

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

25. Post-market clinical follow-up

Part II of the UK MDR 2002, Annexes VIII and X (medical devices) and Part III, Annexes 6 and 7 (active implantable devices) (as modified by Schedule 2A to the UK MDR 2002) and Article 61 of the EU MDR 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.

Northern Ireland

You must notify MHRA of all clinical investigations involving CE marked devices that also involve procedures additional to the normal conditions of use of the device, that are also invasive or burdensome.

The notification should be made at least 30 days before the study commences. MHRA will acknowledge the notification. Should there be any concerns with the proposed study MHRA will write accordingly

The notification will need to include:

- Application form
- Investigators Brochure
- Clinical Investigation Plan
- Signed statement
- REC opinion
- Proof of insurance cover or indemnification of subjects
- Patient Information Sheet and Informed Consent Documentation
- Arrangement to ensure protection and confidentiality of personal data
- Details of the technical documentation (risk analysis, test reports) kept available

Applications are submitted electronically using the Integrated Research Application System (IRAS)

26. Type of investigation

The majority of clinical investigations of medical devices will not include a control group. The decision as to whether a control group is necessary however, will depend on the aims of the investigation. For some devices it would only be possible to demonstrate claims adequately by comparison with a separate or untreated group. If control groups are necessary these should be randomised and prospective, except in exceptional and justifiable circumstances. Pivotal/confirmatory studies should have a control where clinically relevant and appropriate to do so. For all studies, lack of a control group should be justified.

27. End points

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

28. Labelling

All devices intended for clinical investigation must bear the wording ‘exclusively for clinical investigation’ as stated in Part II of the UK MDR 2002, Annex I (13.3(H)) (medical devices) and Part III, Annex 1 (14.1) (active implantable devices) (as modified by Schedule 2A to the UK MDR 2002), and Annex I, chapter III, 23.2(q) of EU MDR. It is recognised that such wording may cause confusion to clinical staff in that it may be thought that the clinical investigation being referred to is of a patient rather than the device. It is therefore recommended that manufacturers draw this requirement to the attention of all clinical investigators, requesting that such investigators ensure that the meaning of this wording is clearly understood by all staff using or coming into contact with the device being investigated and that the device under investigation is segregated, where possible, from any similar devices in routine use. If a device under clinical investigation has been

UKCA/CE marked for another purpose, explanatory labelling to this effect should be attached to the device under investigation.

29. Research ethics committee opinions

For all clinical investigations of devices falling within the scope of the UK MDR 2002 and EU MDR, a relevant Research Ethics Committee (REC) opinion is required (UK MDR 2002: Regulations 16(3) and 29(2) / Article 62.3 EU MDR). This opinion may be obtained in parallel with the MHRA notification. If the REC opinion is not provided at the time the application is made to MHRA, it should be forwarded to the MHRA as soon as it becomes available. No clinical investigation of a non-UKCA/CE marked device should be started until both the relevant REC opinion and the MHRA have raised no grounds for objection.

The MHRA does not accept approvals from independent ethics committees. Manufacturers should seek the opinion of a Research Ethics Committee within the UK Health Departments' Research Ethics Service in all cases.

REC approval is required from just one REC, irrespective of the number of centres participating in the clinical investigation. Further advice on how to apply for a REC opinion can be obtained from the Research Ethics Service. If you require further advice email HRA Queries Line on queries@hra.nhs.uk.

Manufacturers should make it clear, when contacting the Research Ethics Service, that the investigation involves a non-UKCA/CE marked medical device.

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

On occasions it may be helpful for the MHRA to liaise with the relevant ethics committee concerning notifications. Additionally, it can also be helpful for the MHRA to send the Ethics Committee a copy of the final decision for information purposes. For clinical investigations planned to take place in Great Britain, the Clinical Investigation Application Form enables the manufacturer to provide authorisation allowing such communication.

30. HRA approval and confirmed management permission

Each individual site in this clinical investigation must have confirmed management permission. NHS organisations in England provide this by confirming that they have the capacity and capability to take part in the study. In Northern Ireland, Scotland and Wales NHS organisations provide a letter of NHS Permission. Non-NHS organisations should confirm their management permission and receive a favourable Site-Specific Assessment from the Research Ethics Committee. Please note that this clinical investigation must not commence in any UK site until you have received the relevant confirmation for that individual site.

In addition, clinical investigations must not commence in any NHS site in England until they have received HRA Approval.

Full details can be obtained from The Health Research Authority website or by emailing queries@hra.nhs.uk. When seeking advice from the Health Research Authority you should make it clear that the investigation involves a non-UKCA/CE marked medical device.

How your application will be handled by the MHRA

Please refer to our guidance on compiling a submission to MHRA for information on the submission process and documentation requirements.

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

During the assessment experts will assess the safety and performance of the investigational device as well as the design of the clinical investigation to be carried out. MHRA will write if further information is required. Should the nature of the requested information be unclear, it is essential that the manufacturer/sponsor contacts the MHRA as soon as possible to request clarification. Where possible a teleconference will be arranged for a better understanding and to find a resolution within the assessment period, if there are possible grounds for objection.
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For Great Britain, the 60-day clock does not stop when additional information is requested. This applies in all circumstances, including notifications made that cover prolonged holiday periods such as Christmas or New Year.

Northern Ireland

Depending on whether we consult experts, MHRA will provide a decision within 45 or 65 calendar days. This period will be suspended in the event that we request additional information for a maximum of 7 calendar days for each request, up to a maximum of 3 requests. Any further requests will not result in a clock stop.

A letter will be sent to the sponsor by the final day or before with a decision as to whether or not the proposed clinical investigation has been authorised and can be carried out.

31. General requirements

Manufacturers or UK Responsible Persons (or Authorised Representative's for studies in NI) are required to submit initially certain information and to undertake to make available subsequently, if requested by the MHRA, information as specified in Regulations 16 and 29 and Part II, Annexes VIII and X (medical devices) and Part III, Annexes 6 and 7 (active implantable devices) of the UK MDR 2002 (as modified by Schedule 2A to the UK MDR 2002), and Chapter II of Annex XV of the EU MDR.

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

32. Validation of Application: Initial receipt of documentation

Terminology note: In MHRA clinical investigations guidance, where an application is 'valid', this refers to when MHRA has given formal acceptance of the application ('notice') under UK MDR Regulation 16 / 29 (see point (a), below), and the 60-day review period has commenced.

Where an application is 'invalid', this refers to where the application has not received formal acceptance under these regulations (see point (b), below).

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

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

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

b) 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.

For Great Britain, day 1 of the 60 day statutory review period is taken as being the first working day that follows the date MHRA acknowledges receipt of a valid Notification. Validation will be confirmed within 5 calendar days and where a notification is found to be invalid the 60 days will not commence.

Northern Ireland

When MHRA has received your documents and validated them, we will write to you within 10 calendar days to confirm that the application is valid and the assessment has started or we will let you know if there are any issues. If there are any issues raised,
we will confirm these in writing and provide a 10 calendar day deadline for a response. The assessment will not start until we have received a valid response. If, after receipt of the response or the 10 day deadline has expired, the application is still considered to be invalid we will write to confirm this within 5 calendar days.

Day 1 of the MHRA assessment is taken as being the date that we confirm that we have received a valid application.

The MHRA do not accept notifications for clinical investigation or study amendments during the Christmas shutdown period. The exact dates affected will be posted on the MHRA website each year.

33. Expert assessors

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

Assessors from outside the MHRA will have signed a statement of confidentiality incorporating a declaration of any conflict(s) of interest. In addition, every effort will be made to ensure that no conflict of interest will arise for an expert assessor in relation to any aspect of the clinical investigation that he/she is asked to assess by the MHRA. In the interests of confidentiality however, manufacturers may, at the time of the original submission, name the institutions/individuals whom they may not wish to act as assessors for the investigation in question and provide the rationale. The MHRA will, so far as possible, bear such views in mind when appointing assessors. Submitted documents are shared with assessors via a secure portal and all assessors are required not to retain any copies.

34. Additional information

Each expert assessor will be allowed 14 days in which he/she will be able to request, through the MHRA, any further information that he/she thinks necessary in order for a proper assessment of the proposed clinical investigation to be made with regard to his/her area of expertise. This additional information may comprise either part or the whole of the information which the

manufacturer must undertake to keep available for the MHRA (Regulations 16 and 29 of the UK MDR 2002 and Part II, Annexes VIII and X (medical devices) and Part III, Annexes 6 and 7 (active implantable devices) of the UK MDR 2002 (as modified by Schedule 2A to the UK MDR 2002), and Chapter II of Annex XV of the EU MDR. It is in the interests of the manufacturer to supply this additional information as soon as possible if it is requested, so that an adequate assessment of all relevant data can be completed. For Great Britain, the 60-day clock will not stop whilst this requested information is being assembled.

Northern Ireland

For Northern Ireland the 45 or 65 day review period will be paused for the first 3 requests for additional information for a maximum of 7 calendar days for each request. Any further requests will not result in a clock stop.

35. 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 whereby the proposed clinical investigation should not proceed, the MHRA will notify the applicant of this decision.

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

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

- where there are reasonable grounds to suspect that a device does not satisfy relevant essential requirements / general safety and performance requirements; or
- where there are reasonable grounds to suspect that the clinical investigation is not subject to controls equivalent to the requirements of ISO 14155:2020; or
- where there exists expert professional opinion on the proposed clinical investigation that the risk benefit analysis given by or on behalf of the manufacturer is inaccurate and that, were the investigation to take place, there would be a significant probability of serious illness, injury or death to the patient or user; or
- where there is inadequate/incomplete pre-clinical or animal data in order to make it reasonable for clinical testing to commence, or
- where insufficient information has been submitted to enable a proper assessment of the safety aspects of the proposed clinical investigation to be made; or
- where the manufacturer/sponsor has delivered any documentation necessary for the assessment so late that insufficient time remains within the assessment period for the MHRA to complete its assessment.

Northern Ireland

For the purposes of Northern Ireland, if the MHRA raises grounds for objection, it will notify EU Competent Authorities and the European Commission, where necessary, of the decision and grounds for objection. The grounds for objection will otherwise remain confidential between the expert assessors, the manufacturer, the HRA and the ethics committee.

The applicant may re-submit revised documentation pertaining to the proposed clinical investigation, provided the reason for refusal of the original application has been addressed. An

appropriate fee, as defined in the UK MDR 2002 will need to accompany the subsequent notice addressing the grounds for objection and a copy of the full documentation along with the completed Clinical Investigation Application Form via IRAS should be provided. Any further questions or issues raised by the MHRA will only be in relation to the information supplied to address the original grounds for objection. This, however, is only valid provided the documentation remains the same with the exception of that addressing the grounds for objection, unless the further information raises safety issues or a significant change to the risk/benefit analysis which impinge on the original protocol. Therefore, a covering letter should be provided with the resubmission stating that the documentation does not differ from that provided with the original submission or as amended during the MHRA assessment, except in sections that address the original grounds for objection.

Northern Ireland

For Northern Ireland, where a resubmission is being made for an application originally submitted under the MDD, MHRA may also request changes are made to the study documentation to bring the study into compliance with the Medical Device Regulations 2017/745.

When making a resubmission please provide:

1. Any necessary documents to address the grounds for objection including red lined (showing changes made) and clean copies of all amended study documentation;
2. A covering letter stating that the documentation does not differ from that provided with the original submission or as amended during the MHRA assessment, except in sections that address the original grounds for objection. Please include in the covering letter an explanation as to how the grounds for objection have been addressed within the documentation;
3. A revised Clinical Investigation Application Form. Update the Clinical Investigations Application form and documents in the original project on IRAS to reflect changes made to address the grounds for objection. This will keep the IRAS reference number the same for the re-submission;
4. A copy of the original notification documentation (with the exception of those documents revised in point 1 above) for reference only.

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

Fees for resubmission are set out on our website.

36. Amendments/Modifications

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

- covering letter with:
    - the MHRA reference number for the clinical investigation

  - a table with a summary of each proposed change to the clinical investigation plan/design of device/other study documentation, with the reason for each change

- red lined (showing changes being made) and clean copies of all amended study documentation
- details of who to invoice (full company name, address and registered tax/VAT number)
- 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.

Northern Ireland

All proposed changes must be notified to MHRA, however only those considered to be substantial will require authorisation. Substantial modifications must not be implemented until MHRA have confirmed authorisation. Depending on whether MHRA consult experts, MHRA will issue a decision within 38 or 45 calendar days.

Definitions of what MHRA consider to be substantial and non-substantial modifications are provided in the glossary of terms.

The MHRA retains the right to request a new clinical investigation notification if the amendments/modifications are thought to increase the risk to either the patient or the user, or if the MHRA considers that the amendments negatively impact the reliability and robustness of the data generated, and/or constitute a new investigation in accordance with Regulation 56(3) of the UK MDR 2002.

Where being undertaken, feasibility / pilot studies should be complete before conducting a pivotal study. Increases to the sample size and/or number of centres participating in the study will only be considered with appropriate justification.

37. Final clinical investigation report

Manufacturers/sponsors are required to notify the MHRA when a clinical investigation comes to an end as stated in Regulations 16(11) and 29(10) of the UK MDR 2002 and Article 77 of EU MDR. The MHRA should be provided with a copy of the final clinical investigation report within 1 year of the end of the clinical investigation.

38. Early termination or temporary halt 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 as stated in Regulations 16(11) and Section 29(10) of the UK MDR 2002. The MHRA may request a copy of the final written report of a clinical investigation of a device falling within the scope of the UK MDR 2002 (Regulations 16(10) and 29(9)).

Northern Ireland

Sponsors are required to notify the MHRA of the temporary halt or early termination of a clinical investigation and provide a justification within 15 days, or 24 hours if the decision was taken on safety grounds. The clinical investigation report and summary must be provided within 3 months for such studies that are temporarily halted or terminated early.

39. Adverse events involving devices undergoing clinical investigation

Regulation 16(10)(a) and Part II, Annex X of the UK MDR 2002 (as modified by Part II of Schedule 2A to the UK MDR 2002) require manufacturers to record fully all adverse events and report all serious adverse events occurring in all participating centres to the MHRA.

A 'serious adverse event' is one which:

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

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

All serious adverse events, whether initially considered to be device related or not, involving a device under clinical investigation coming within the scope of the UK MDR 2002 and undergoing clinical investigation, should be reported to the MHRA (Part II, Annexes VIII and X, Para 2.3.5 (medical devices) and Part III, Annex 7, Para 2.3.5 (active implantable devices) (as modified by Schedule 2A to the UK Medical Devices Regulations 2002)). Such events also include those arising out of the same investigation being carried out in other countries since such events may have a direct influence on the status of the investigation. These reports should initially be made as soon as possible and should not be delayed while the manufacturer attempts to gain access to, or test, the device or make a full investigation. The results of the full investigation should be made available later as appropriate.

MEDDEV 2.7/3 provides guidance on the requirements for reporting serious adverse events with timelines and provides a template form to use for this purpose. This document can be downloaded from: http://ec.europa.eu/growth/sectors/medical-devices/guidance/.

Submit an SAE reporting form in the new MORE portal with your completed table attached. See details on how to register for the MORE portal.

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

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

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 (UK MDR 2002: Regulation 16(6) and Regulation 29(5)).

Northern Ireland

Sponsors are required to fully record all adverse events and report the following events occurring in all participating centres to the MHRA:

(a) any serious adverse event that has a causal relationship with the investigational device, the comparator or the investigation procedure or where such causal relationship is reasonably possible;

(b) any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate;

(c) any new findings in relation to any event referred to in points (a) and (b).

These should be provided using the MDCG 2020-10/2 SAE reporting table.

Submit an SAE reporting form in the new MORE portal with your completed table attached. See details on how to register for the MORE portal.

'serious adverse event' means any adverse event that led to any of the following:

(a) death,

(b) serious deterioration in the health of the subject, that resulted in any of the following:

(i) life-threatening illness or injury,

(ii) permanent impairment of a body structure or a body function,

(iii) hospitalisation or prolongation of patient hospitalisation,

(iv) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

(v) chronic disease,

(c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect;

40. Study deviations

Manufactures must notify the MHRA of all deviations to the study as soon as they have been made aware of them. Details about the nature of the deviation, when it occurred, where it occurred, and any proposed corrective actions should be provided.

Use the following MHRA protocol deviation tracker Excel template when reporting deviations and keep this as a 'live' document so that new deviations can be added. This enables both the sponsor and MHRA to have a complete overview each time it is submitted.

Send the completed spreadsheet to the MHRA via email at info@mhra.gov.uk.

41. MHRA actions / Corrective measures

Where there are grounds for considering that the requirements of the regulations are not met, MHRA can:

- Withdraw the no objection letter / Revoke authorisation
- Suspend or terminate the clinical investigation
- Require the sponsor to modify any aspect of the clinical investigation

If such action is deemed necessary, MHRA will write to the manufacturer/sponsor to inform them of the decision and agree any further actions that may be necessary.

42. UKCA/CE marking

Please inform MHRA in the event that the medical device under investigation is UKCA/CE marked. We request that at the same time MHRA are also provided with a summary report of the clinical data from this clinical investigation that was used to support the UKCA/CE mark.

If the UKCA/CE marking covers the purpose under investigation, further amendments to the study documentation can be made without notification to MHRA.

43. Other MHRA guidance notes

The MHRA has other guidance documents relevant to clinical investigations. These include the following which can all be found here:

- Clinical investigations of medical devices – compiling a submission to MHRA
- Clinical investigations of medical devices – guidance for investigators
- Clinical investigations of medical devices – biological safety assessment
- Clinical investigations of medical devices – statistical considerations

Any queries regarding this document or the clinical investigation procedure should be directed to info@mhra.gov.uk.

Glossary of terms

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

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

Adverse device event
means a device-related adverse incident.

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

Clinical benefit

'clinical benefit' means the positive impact of a device on the health of an individual, expressed in terms of a meaningful, measurable, patient-relevant clinical outcome(s), including outcome(s) related to diagnosis, or a positive impact on patient management or public health.

Clinical evidence
'clinical evidence' means clinical data and clinical evaluation results pertaining to a device of a sufficient amount and quality to allow a qualified assessment of whether the device is safe and achieves the intended clinical benefit(s), when used as intended by the manufacturer.

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

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

Clinical performance
'clinical performance' means the ability of a device, resulting from any direct or indirect medical effects which stem from its technical or functional characteristics, including diagnostic characteristics, to achieve its intended purpose as claimed by the manufacturer, thereby leading to a clinical benefit for patients, when used as intended by the manufacturer.

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

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

Implantable device
means any device which is intended to be totally introduced into the human body, or to replace an epithelial surface or the surface of the eye, by surgical intervention and which is intended to remain in place after the procedure. Any device intended to be partially introduced into the human body

through surgical intervention and intended to remain in place after the procedure for at least thirty days is also considered an implantable device.

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

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

Medical device

'medical device' means any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

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

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

For Great Britain, the applicable definition of a medical device may be found in UK MDR Regulation 2.

For Northern Ireland, the applicable definition may be found in Article 2(1) of the EU MDR.

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

Non-Substantial modification

Non-substantial modifications are changes that are unlikely to have a substantial impact on the safety, health or rights of the participants or on the robustness or reliability of the clinical data generated by the investigation and include:

- a change of sponsor(s) or sponsor's legal representative;
- a change to the insurance or indemnity arrangements for the study;
- minor changes to the protocol or other study documentation, e.g. correcting errors, updating contact points, minor clarifications;
- changes to the chief investigator's research team
- changes to the research team at particular trial sites (other than appointment of a new principal investigator);
- changes in funding arrangements;
- minor changes in the documentation used by the research team for recording study data;
- changes in the logistical arrangements for storing or transporting samples;

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

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

Relevant General Safety and Performance Requirements
means the general safety and performance requirements, or such aspects of the general safety and performance requirements as apply to a specific device.

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

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

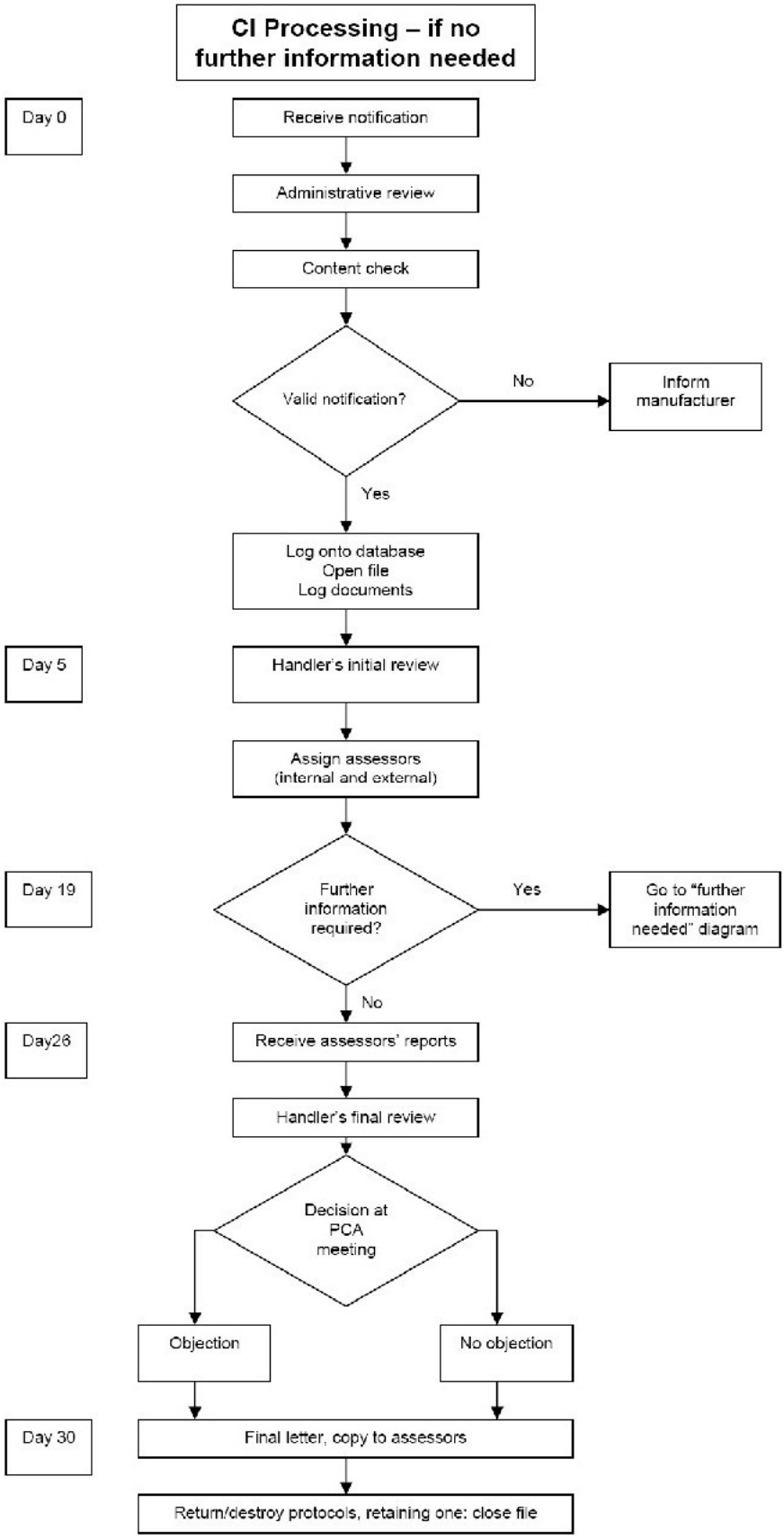
Substantial modification

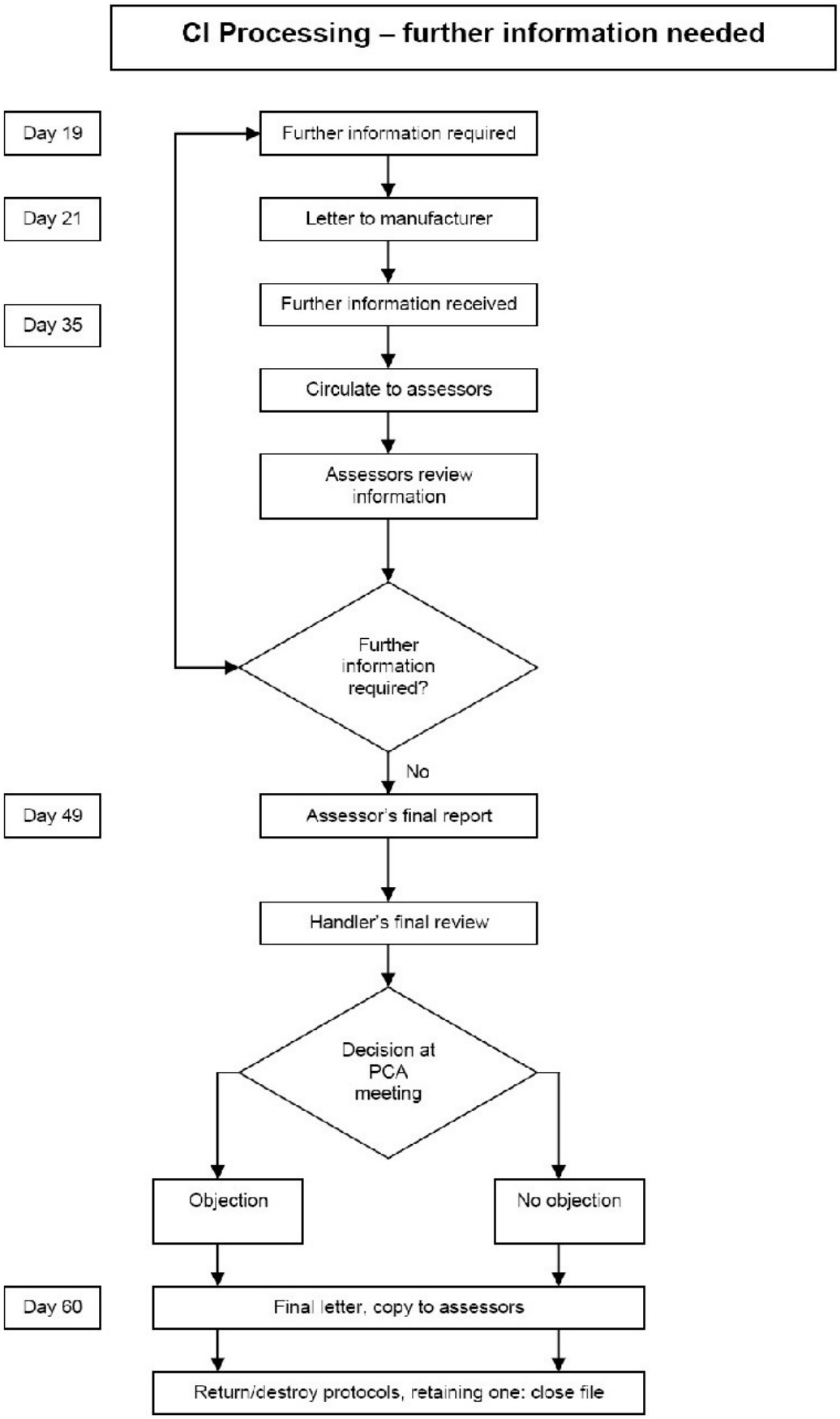
Substantial modifications are changes that are likely to have a substantial impact on the safety, health or rights of the participants or on the robustness or reliability of the clinical data generated by the investigation and include:

- changes to the medical device under investigation
- changes to the design or methodology of the clinical investigation, or to background information.
- changes to the procedures undertaken by participants;
- changes to the risk/benefit assessment for the study;
- significant changes to study documentation such as clinical investigation plan, investigator's brochure, participant information sheets, consent forms, letters to GPs or other clinicians, information sheets for relatives or carers;
- appointment of a new chief investigator
- inclusion of a new trial site (not listed in the original application)
- appointment of a new principal investigator at a trial site
- temporary halt of a study to protect participants from harm, and the planned restart of a study following a temporary halt;
- a change to the definition of the end of the study;
- extension of the study beyond the period specified in the application form.
- any other significant change to the protocol
- changes requested by an ethics committee

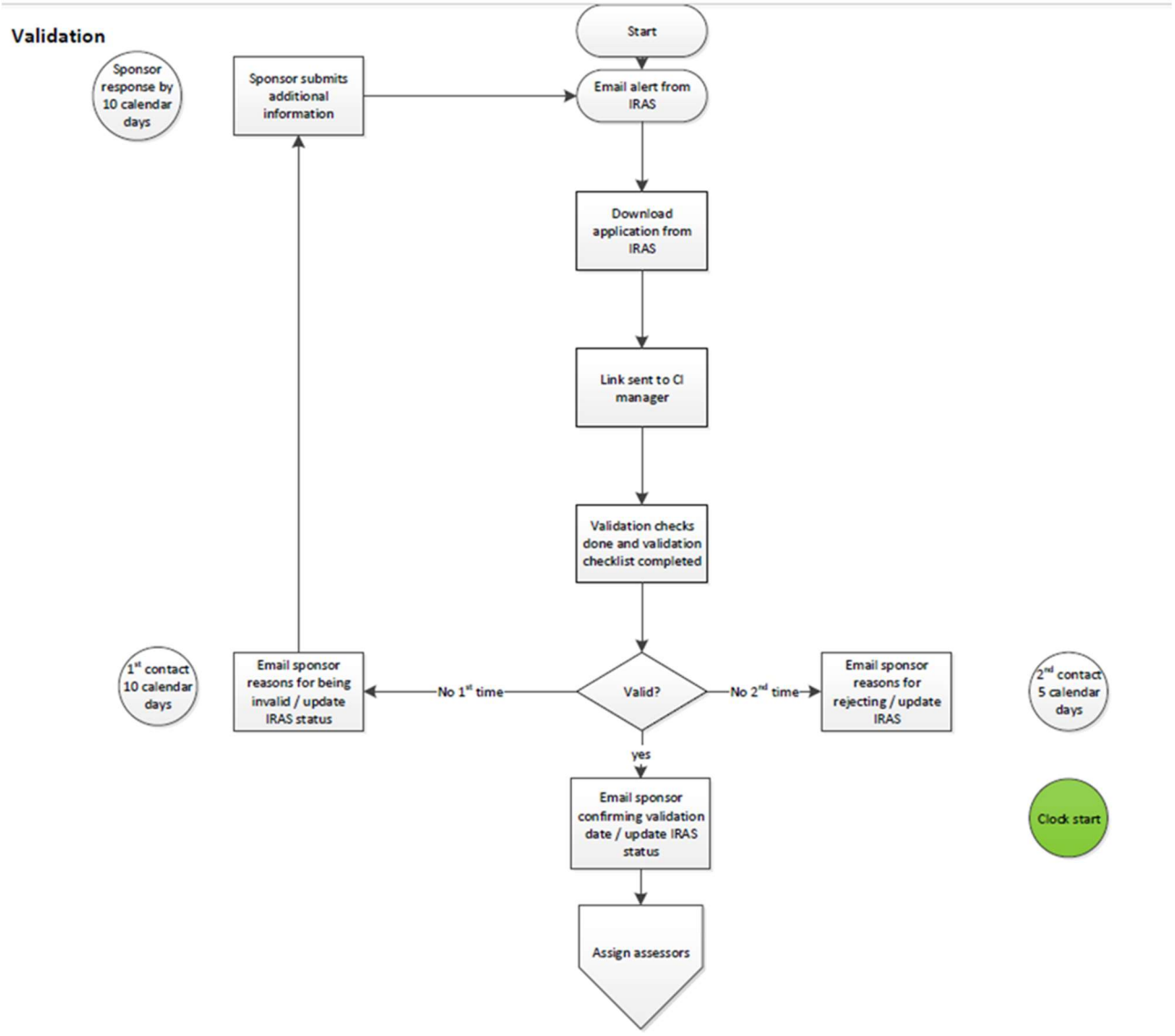
Surgically invasive
means an invasive device which penetrates inside the body, other than through an established body orifice, with the aid or in the context of a surgical operation.

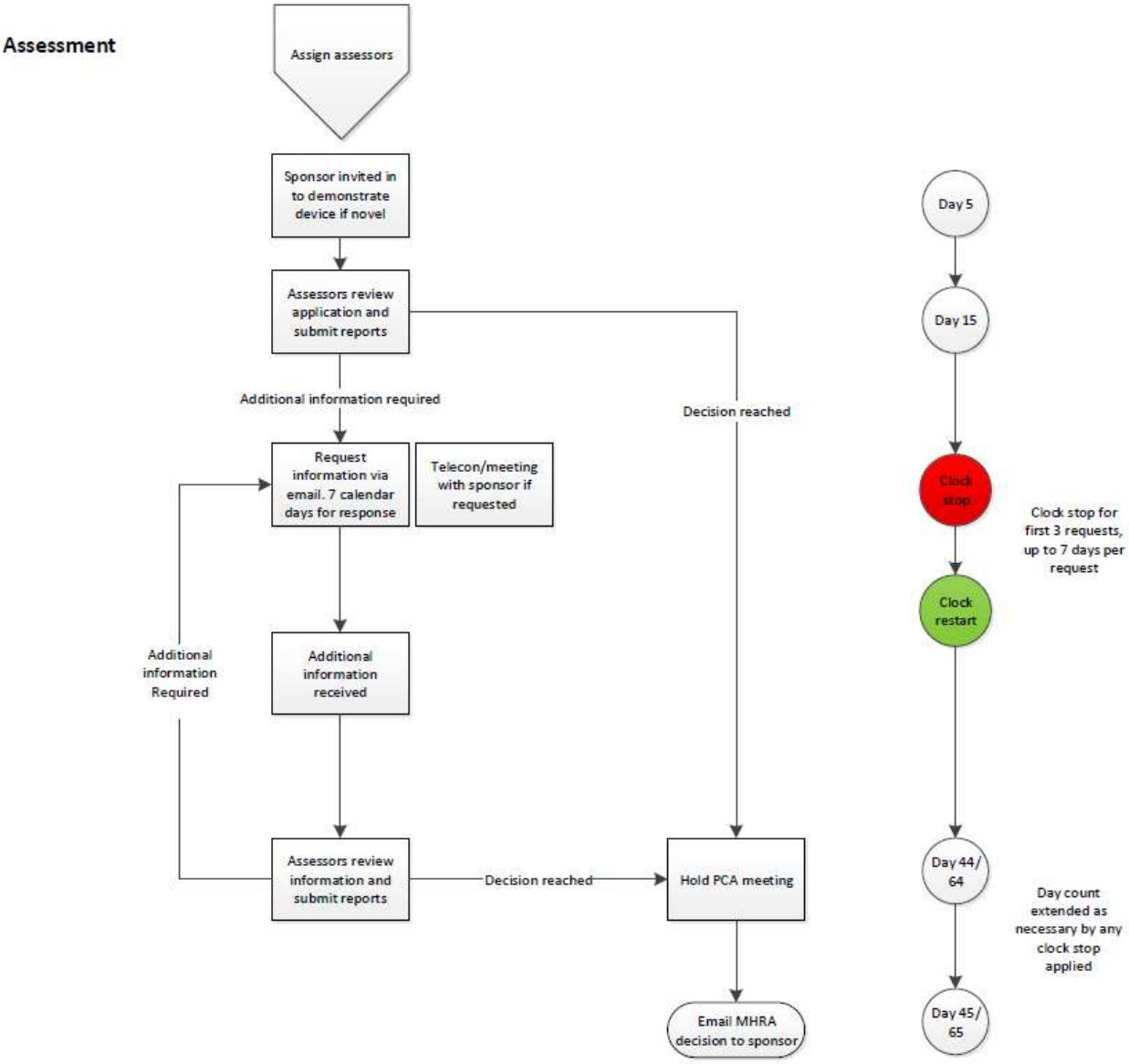
Appendix 1 Flow diagrams of how the MHRA processes clinical investigations in Great Britain




CI Processing – further information needed
Day 19
Further information required
Day 21
Letter to manufacturer
Day 35
Further information received
Circulate to assessors
Assessors review information
Further information required?
No
Day 49
Assessor's final report
Handler's final review
Decision at PCA meeting
Objection
No objection
Day 60
Final letter, copy to assessors
Return/destroy protocols, retaining one: close file

Appendix 2 Flow diagrams of how the MHRA processes clinical investigations involving Northern Ireland


Validation
Start
Sponsor response by 10 calendar days
Sponsor submits additional information
Email alert from IRAS
Download application from IRAS
Link sent to CI manager
Validation checks done and validation checklist completed
1st contact 10 calendar days
Email sponsor reasons for being invalid / update IRAS status
No 1st time
Valid?
No 2nd time
Email sponsor reasons for rejecting / update IRAS
2nd contact 5 calendar days
yes
Email sponsor confirming validation date / update IRAS status
Clock start
Assign assessors


Assessment
Assign assessors
Sponsor invited in to demonstrate device if novel
Assessors review application and submit reports
Additional information required
Decision reached
Request information via email. 7 calendar days for response
Telecon/meeting with sponsor if requested
Additional information Required
Additional information received
Assessors review information and submit reports
Decision reached
Hold PCA meeting
Email MHRA decision to sponsor
Day 5
Day 15
Clock stop
Clock stop for first 3 requests, up to 7 days per request
Clock restart
Day 44/ 64
Day count extended as necessary by any clock stop applied
Day 45/ 65