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

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1. PURPOSE

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

It should be used in conjunction with RGIT_SOP_002 'Ethics Approval for Health-Related Research, RGIT_SOP_003 on 'Applying for NHS REC Approval' and the RGIT_SOP_039 'Health Research Authority for Research Studies'

2. INTRODUCTION

The UK Medical Devices Regulations came into force in June 2002 and incorporate the provisions of the Medical Devices Directive 93/42/EEC, the Active Implantable Medical Devices Directive 90/385/EEC and the In Vitro Diagnostic Medical Devices Directive 98/79/EEC.

A copy of the [directive \(cited on 20 Mar 2023\)](#) can be found on the [Europa website \(cited on 20 Mar 2023\)](#).

A number of additional Directives amending the original Directive have since been introduced; further details can be found on [Medical devices regulation and safety: detailed information \(cited on 20 Mar 2023\)](#).

These current regulations establish systems under which a manufacturer must submit to the UK Competent Authority for approval for clinical investigations of medical devices to be carried out in the UK. The UK Competent Authority is the [Medicines and Healthcare products Regulatory Authority \(MHRA\) \(cited on 20 Mar 2023\)](#). The aims of these regulations are to ensure the safety and performance of medical devices, and to prohibit the marketing of devices that might compromise the health and safety of patients, users or any relevant 3rd party.

The above directives are given effect in UK law through the Medical Devices Regulations 2002, these regulations continue to have effect in Great Britain..

It should be noted that in EU member states including Northern Ireland, the Regulation 2017/745 on (EU MDR) was applied on 26th May 2021, and the Regulation 2017/746 on (EU IVDR)s. was applied on 26th May 2022. These do not apply to Great Britain.

2.1. Is it a device?

In the [Medical Devices Directive \(MDD\) \(cited on 20 Mar 2023\)](#), a medical device is described as any instrument, apparatus, appliance, software, material or other article used alone or combined for humans to:

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

A medical device does not achieve its main intended action by pharmacological, immunological or metabolic means although it can be assisted by these.

If manufacturing a medical device, the specific directive for the product type must be followed as it sets out the essential requirements the product must meet in the interest of patient safety. Further information on what a medical device is can be found in the [MDD \(cited on 20 Mar 2023\)](#).

See the [guidance on borderline products \(cited on 20 Mar 2023\)](#). if you are unsure whether your product is a medicine or a medical device or if it overlaps, [Guidance – Decide if your product is a medicine or a medical device \(cited on 20 Mar 2023\)](#).

As well as medical device apps becoming a growth area in healthcare management in hospital and in the community settings, the role of apps used as part of fitness regimes and for social care situations is also expanding. However, in the UK, standalone software and apps that meet the definition of a medical device are still required to be UKCA marked in line with the Medical Device Regulations 2002 (as amended) (UK MDR 2002) in order to ensure they are regulated and acceptably safe to use and also perform in the way the manufacturer/ developer intends them to. To determine whether an device app constitutes a medical device then please use the [MHRA guidance on apps \(cited on 27 Mar 2023\)](#). In addition, the [NHS AI and Digital Regulations Service for Health and Social Care \(cited on 27 Mar 2023\)](#) provides guidance on understanding the regulations in AI and digital technology in health and social care.

2.2. Recognition of UKCA/CE marking

The UKCA regime has been operational since 1 January 2021 and from this date, where a product is covered by the UKCA marking, the UKCA marking can be placed on a product.

The [MHRA \(cited on 23 Aug 2024\)](#) will accept CE marked devices on the Great Britain market until, at the latest, 30 June 2030 depending on device type and classification.

This guidance has been updated with a [Roadmap \(cited on 23 Aug 2024\) towards the future regulatory framework for medical devices](#) (published 9 January 2024) which sets out intended timescales for delivery of the future core regulations.

2.3. UK responsible person

To place a device on the Great Britain market (England, Wales and Scotland), manufacturers based outside the UK are required to appoint a UK Responsible Person. The UK Responsible Person acts on behalf of the non-UK manufacturer to carry out specified tasks in relation to the manufacturer's obligations. The UK Responsible Person must provide written evidence that they have the manufacturer's authority to act as their UK Responsible Person. UK Responsible Person requirements for the Northern Ireland market are covered [separately](#). Importers and distributors are not required to appoint a UK Responsible Person.

In cases where the Great Britain importer is not the UK Responsible Person, the importer is required to inform the relevant manufacturer or UK Responsible Person of their intention to import a device. In such cases, the manufacturer or the manufacturer's UK Responsible Person is required to provide the MHRA with details of device importers.

3. PROCEDURE

Manufacturers wishing to make an application for pre-clinical assessment of an active implantable medical device or a medical device to be carried out in part or in whole in the UK should apply to the MHRA. To ensure a high level of safety and performance, demonstration of compliance with the general safety and performance requirements laid down in the Regulation should be based on clinical data that, for class III devices and implantable devices should, as a general rule, be sourced from clinical investigations that have

been carried out under the responsibility of a sponsor. It should be possible both for the manufacturer and for another natural or legal person to be the sponsor taking responsibility for the clinical investigation.

- Notification to MHRA is required for clinical investigations involving non-UKCA/non-CE marked/non-CE UKNI devices that are:
 - implantable or a Class III Medical device (please see Medical device classes below)
 - **Class I** – Provided non-sterile or do not have a measuring function (low risk)
 - **Class I** – Provided sterile and/or have a measuring function (low/medium risk)
 - **Class IIa** (medium risk)
 - **Class IIb** (medium/high risk)
 - **Class III** (high risk)
 - is a completely new concept of device in clinical practice
 - where a device contains materials previously untested in humans
 - where in-vivo or animal testing of the device cannot mimic the clinical situation
 - where there is a new manufacturer, especially of a high risk device

Change in intended use of the CE/UKCA/CE UKNI device

- Where a device with CE marking is to be used for a new purpose and eventually to be CE marked for this new purpose, a notification of clinical investigation should be made to the MHRA.

Prototype changes to devices

Where there are a small number of prototype models of a device for clinical investigation to assess safety and efficacy, these changes are regarded as variations and are included in one application, unless the risk to users is increased with these variations. The MHRA may then request a new submission. A notification to MHRA will not be required for medical devices that are CE/UKCA/CE UKNI marked for the purpose under investigation.

Special circumstances for healthcare establishments

You don't need to notify MHRA of a clinical investigation if:

- you have manufactured the medical device in house for your own patients with no objective to place it on the market.

You may need to notify MHRA of a clinical investigation if:

- you want to provide a medical device to another organisation, that up until now has been manufactured in-house for patients, for data to support safety and performance of a commercial product.

See [common scenarios for healthcare establishments](#) (PDF, 71.1KB, 1 page, *cited on 20 Mar 2023*) which may be relevant.

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

A letter will be sent by the 60th day or before with a decision ('objection', or 'no objection') as to whether the proposed clinical investigation can be carried out.

For guidance on whether a Clinical Investigation is required to demonstrate compliance of the device with requirements, the MHRA's Guidance for Manufacturers on Clinical Investigations to be carried out in the UK should be consulted via the website

[Guidance of legislation - Clinical investigations of medical devices - guidance for manufacturers \(cited on 20 Mar 2023\)](#)..

3.1. Making an Application for Pre-Clinical Assessment

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

3.2. How to Apply

A notification to MHRA will not be required for medical devices that are CE/UKCA/CE UKNI marked for the purpose under investigation.

If possible, please provide MHRA with advanced notice of your intention to submit a clinical investigation by emailing devices.regulatory@mhra.gov.uk with some basic details about the investigational device, the intended population, the type of study, and estimated application date. Please provide as much notice as possible. An advanced notice is helpful to MHRA, however is not a substitute for the formal clinical investigation notification.

You need to prepare your documents before you notify MHRA of a proposed clinical investigation.

Applications for approval for a clinical investigation of a medical device should be made via the [Integrated Research Application System \(IRAS\)](#) (cited on 20 Mar 2023). website and completing the Medical Devices form (Clinical Investigation application form). Upload the relevant supporting documents on to IRAS and then follow the instructions on how to submit the application. Documents should ideally be in pdf format.

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

Queries regarding the application process can be made to the Medical Devices Unit at the MHRA via devices.regulatory@mhra.co.uk.

The 60 day assessment period will commence once a valid notification is received by the MHRA. Day 1 of the 60 days is taken as being the first working day that follows the date of receipt of a valid Notification. Validation will be confirmed within 5 working days and where a notification is found to be invalid the 60 days will not commence.

3.3. Cost of Applying

The Medical Devices (Fees Amendment) Regulations 2017 came into force on 1 April 2017. These regulations include the introduction of new fees for amendments to clinical investigations.

You do not need to attach proof of payment to applications. You will receive an invoice to allow you to make payment for the correct amount once your application has been validated. Please note that the IRAS forms still have questions relating to payment to MHRA, however you no longer need to pay in advance of making your application.

The fee rate is based on a single investigational device being used in a study. Where two or more investigational devices are being used and there is no functional relationship between them, the fee will be increased to reflect the additional workload to the MHRA

See the MHRA website for up-to-date fee information.

3.4. Documentation Required

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

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

- Covering letter on headed paper
- Clinical investigation plan in line with ISO14155
- Investigator's brochure in line with ISO14155
- Participant information sheet

Participant information should identify and explain all risks to participants.

- Participant consent form
- CVs for UK clinical investigators
- Device details

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

- Essential requirements checklist
- Risk analysis

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

- Instructions for use of a medical device

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

- Device labels

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

- Summary of all bench testing and pre-clinical testing conducted
- Summary of all clinical experience with the device to date

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

- End of study reports for any concluded clinical investigations that involved the same medical device under investigation

- List of standards met
- Sterilisation validation report (where relevant)

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

- Software information (where relevant)
- Biological safety assessments of patient contacting materials (where relevant)
- Information on animal tissues (where relevant)
- Information on any medicine or human blood derivative incorporated into the device
- Research ethics committee opinion (if available)

Information on documentation required for submission can be found in the ['Clinical investigations of medical devices – compiling a submission to MHRA'](#) document [\(cited on 20 Mar 2023\)](#).

3.5. MHRA Processing of Approval Application

3.5.1 Initial receipt of documentation

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

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

3.5.2 Expert Assessors

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

3.5.3 Additional Information

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

3.5.4 MHRA Decision

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

If the MHRA consider that the proposed investigation may present unjustifiable risks to public health or safety, the MHRA will notify the applicant of its objection to the commencement of the proposed clinical investigation.

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

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

If the application raises grounds for objection, it is possible to re-submit revised documentation, so long as the reason for refusal of the original application has been addressed.

It is advised that you arrange a meeting or conference call with the MHRA prior to re-drafting a clinical investigation resubmission to ensure that they understand the original concerns.

3.5.5 Additional Approvals

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

3.5.6 ICHT New Interventions Committee

For device studies occurring at Imperial College Healthcare NHS Trust, a copy of the protocol should be sent to the Trust [New Interventions Committee \(cited on 20 Mar 2023\)](#), for review prior to seeking ethics and regulatory approval:

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

3.6. Changes or Modifications to the Protocol

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

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

3.7. Final Written Report

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

3.8. Adverse incidents involving devices undergoing clinical investigation

All serious adverse incidents must be reported to the MHRA, whether it is initially thought to be device related or not. If adverse events arise out of the same investigation being carried out in other EU countries they should also be reported to the MHRA, as they may have a direct influence on the status of the UK investigation. Such reports should be made as soon as possible and should not be delayed while the manufacturer attempts to gain access to, or test, the device or make a full investigation.

The MHRA have the right to withdraw their approval, if it decides that the serious adverse events give rise to issues of public health.

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

The MHRA may authorise the use of individual non-CE/UKCA/UKNI-marked devices falling within the scope of the Medical Devices Regulations on humanitarian grounds, provided that they are satisfied that such use would be in the best interests of the patient and the protection of health.

In such cases, the device may not be used until an application requesting such use has been made by the manufacturer and due authorisation has been given by the MHRA. The MHRA's approval only applies to the use of the individual device for a named individual within the UK. Failure to comply with these requirements constitutes a criminal offence. For full details of the humanitarian use of non-CE marked devices, together with the relevant forms may be found on the MHRA website – Medical devices regulation and safety, [Guidance Exceptional use of non-CE marked medical devices \(cited on 20 Mar 2023\)](#)..

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

Devices.Regulatory@mhra.gov.uk

4. REFERENCES

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[Notify the MHRA about a Clinical Investigation of a Medical Device \(cited on 20 Mar 2023\)](#)

[MHRA Guidance on the Biological Safety Assessment \(cited on 20 Mar 2023\)](#)

[MHRA Medical Devices: Conformity and CE mark \(cited on 20 Mar 2023\)](#)

[MHRA Using the UKCA Marking \(cited on 24 Apr 2023\)](#)

[MHRA Clinical investigations of medical devices –guidance for manufacturers \(cited on 20 Mar 2023\)](#)

[Guidance document - Classification of Medical Devices - MEDDEV 2.4/1 rev.9 \(cited on 20 Mar 2023\)](#)

[93/42/EEC Medical Devices Directive \(cited on 20 Mar 2023\)](#)

[EEC Active Implantable Medical Devices \(cited on 20 Mar 2023\)](#)

[EEC In Vitro Diagnostic Directive \(cited on 20 Mar 2023\)](#)

[EEC Community Code relating to medicinal products for human use \(cited on 20 Mar 2023\)](#)

[REGULATION \(EU\) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation \(EC\) No 178/2002 and Regulation \(EC\) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EE \(cited on 20 Mar 2023\)](#)

[Annex III of the Commission Recommendation \(2013/473/EU\) of 24 September 2013 \(cited on 20 Mar 2023\)](#)

[MHRA Medical Devices: Software Applications \(apps\) \(cited on 27 Mar 2023\)](#)

[NHS AI and Digital Regulations Service for Health and Social Care \(cited on 27 Mar 2023\)](#)

[Roadmap towards the future regulatory framework for medical devices \(cited on 23 Aug 2024\)](#)

5. APPENDICES

The following Appendices list the following Templates associated to this SOP which can be found on the [SOP, Associated Documents & Templates page \(cited on 20 Mar 2023\)](#).

Appendices 1-4 have been combined into the RGIT_TEMP_028 Guidance Notes for Medical Devices

Appendix 1: Guidance notes on medical devices incorporating tissues of animal origin

Appendix 2: Guidance Notes on Clinical Investigations of Active Devices

Appendix 3 - Medical devices: conformity assessment and the UKCA/CE mark