Guidance on legislation

Clinical investigations of medical devices – guidance for investigators

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Medicines and Healthcare Products Regulatory Agency

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This document replaces Guidance Note 3 ‘Information for clinical investigators’

Revision history

This version	Date published	Changes
V1.0	November 2013	n/a
V1.1	January 2021	To align with end of transition period
V1.2	May 2021	Updated with references to EU MDR for Northern Ireland

Introduction

The purpose of this document is to help clinical investigators by highlighting a number of specific requirements that arise in relation to the clinical investigation of non-UKCA/CE/CE UKNI marked medical devices.

In order to demonstrate compliance with the essential requirements of the UK Medical Devices Regulations 2002 (SI 2002 No 618, as amended)(UK MDR 2002) and the general safety and performance requirements of the (EU) Medical Devices Regulation 2017/745 (MDR) governing safety and performance, and in order to justify the application of UKCA/CE/CE UKNI marking, it will sometimes be necessary for the manufacturer of the device to provide clinical data with which to back up claims made for that device. This may involve the need for a specifically designed clinical investigation 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 and to assess whether these are acceptable risks when weighed against the intended performance of the device.

If such an investigation is necessary, the manufacturer must make an application to the MHRA before the investigation is due to begin, and such a clinical investigation may only proceed provided no grounds for objection are raised by the MHRA within the statutory review time constraint. The MHRA will reach a decision aided by a number of expert assessors. It is the responsibility of the manufacturer both to notify the MHRA and to submit the documentation required by the UK MDR 2002 or EU MDR to the MHRA. The clinical investigator will normally have no direct contact with the MHRA.

It is a criminal offence for a person to supply a device which does not carry the UKCA/CE/CE UKNI marking, save in the defined exceptions of devices intended for clinical investigation, custom-made devices, or those with an exemption.

1 Research ethics committee approval

For all clinical investigations of devices falling within the scope of the UK MDR 2002, Part II for medical devices, or Chapter VI of EU MDR, a relevant ethics committee opinion is required. This opinion should be sought either before or in parallel with the notification to the MHRA, normally by the investigator. The manufacturer will be required to submit a copy of the research ethics committee approval to the MHRA.

The MHRA does not accept approvals from independent ethics committees. The manufacturer should seek the opinion of an ethics committee appointed by the Research Ethics Service (RES) in all cases unless it can demonstrate why RES-appointed committees would not assess their clinical investigation. In such cases the manufacturer will need to demonstrate that any independent ethics committee appointed was constituted in line with RES guidelines. However, please note that RES will review all clinical investigations due to be conducted outside the NHS and therefore situations where an independent ethics committee is required are not foreseen.

Clinical investigators, however, should be aware that under the provisions of the UK MDR 2002 and EU MDR, a clinical investigation may not proceed if grounds for objection have been raised by the MHRA, even if approval has been granted by a research ethics committee. All RES appointed ethics committees are aware of this requirement.

2 Grounds for objection

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 manufacturer of its objection to the commencement of the proposed clinical investigation and the reasons for this decision. Circumstances in which the MHRA considers that such risks may exist include:

- where there exists a professional opinion, which states that the risk—benefit analysis 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

- that there are reasonable grounds to suspect that the performance of the device is not that claimed by the manufacturer

or

- where insufficient information has been submitted in order to make a proper assessment of the safety aspects of the proposed clinical investigation.

If the MHRA raises objections to the investigation, the manufacturer should inform the clinical investigator of this. The MHRA will not contact the clinical investigator directly although it may contact the ethics committee.

The manufacturer may re-submit an application for a proposed clinical investigation, provided the reason(s) for refusal of the original submission are addressed.

3 Conduct of a clinical investigation

MHRA expect that the principles of ICH Good Clinical Practice are followed.

Sponsors and investigators must ensure that the investigation is conducted in full accordance with the approved clinical investigation plan (CIP) and the requirements of the UK MDR 2002 or EU MDR. Deviations from the CIP must be reported to MHRA.

There must be adequate monitoring in place to ensure that the rights, safety and well-being of subjects are protected.

All information relating to the clinical investigation must be recorded, processed and stored by the sponsor or investigator in such a way that it can be interpreted and reported, and not impact upon the confidentiality of the records and personal data of the subjects. The personal data of the subjects must be protected in line with General Data Protection Regulations.

There must be an emergency procedure to enable immediate identification of the devices within the investigation – this may be required in the event of an immediate recall of the devices.

4 Labelling of medical devices

All devices intended for clinical investigation must bear the wording ‘exclusively for clinical investigation’. To avoid misunderstandings as to the nature of the clinical investigation, i.e. that it is the device under investigation and not the patient, all clinical investigators should ensure that the meaning of this wording is clearly understood by all staff using or coming into contact with the device and that it is segregated, where possible, from devices in routine use. In some cases, the clinical investigator may consider it necessary to attach appropriate warning signs to the device under investigation.

Devices intended for clinical investigation should not bear the UKCA/CE/CE UKNI marking.

5 Amendments/modifications

All proposed changes to the clinical investigation whether relating to the device, aspects of the clinical investigation plan, investigators or investigating institutions must be notified to the MHRA.

6 Adverse incidents

Any adverse incident involving a medical device undergoing clinical investigation should be reported to the manufacturer, or directly to the Medicines & Healthcare Products Regulatory Agency via the online system AITS@mhra.gov.uk

6 Humanitarian use of non-UKCA/CE/CE UKNI marked devices

The use of an individual non-UKCA/CE/CE UKNI marked device 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 protection of health. In such cases, the device may not be used until an application is made by the manufacturer to the MHRA for such use and due authorisation is 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 UKNI/CE marked device the manufacturer and clinician must fill in a form, which is available on this web page.

7 Further information

Designated standard ISO14155 Clinical investigation of medical devices for human subjects — Good clinical practice, sets out the recommended procedure for a clinical investigation of a medical device. Copies of this standard are obtainable from the British Standards Institution http://www.bsigroup.co.uk/

Further details of the clinical investigation system and the system for reporting serious adverse events of devices undergoing clinical investigation can be obtained by emailing info@mhra.gov.uk

8 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 event.

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

Clinical investigation
means any systematic investigation or study in human subjects, 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 investigator
means the person responsible for the conduct of a clinical investigation and who takes the responsibility for the health and safety of the subjects 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.

Local 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

means any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, together with any accessories, including the software intended by its manufacturer to be used specifically for diagnostic or therapeutic purposes or both and necessary for its proper application, which –

a) is 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,

b) does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, even if it is assisted in its function by such means;

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

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

Principal clinical investigator
means a clinical investigator appointed by the manufacturer to co-ordinate the work in a multicentre clinical investigation or the work of several clinical investigators at one site.

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.

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

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 Documentation required for all clinical investigation submissions

The following list provides an overview of the information that manufacturers should include in the initial submission to MHRA. Detailed guidance on the information required is provided in “Clinical investigations of medical devices – compiling a submission to MHRA”.

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