Guidance on legislation

Clinical investigations of medical devices – guidance for investigators

November 2013

Medicines and Healthcare Products Regulatory Agency

Contents

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

Revision history

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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-CE marked medical devices.

In order to demonstrate compliance with the essential requirements of the EC directives governing safety and performance, and in order to justify the application of CE-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 competent authority (the MHRA) at least 60 days 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 60-day 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 Directives 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 CE marking, save in the defined exceptions of devices intended for clinical investigation or custom-made devices. In this respect there is no equivalent for medical devices of the ‘named patient’ special supply on prescription from a doctor as exists for pharmaceuticals.

1 Research ethics committee approval

For all clinical investigations of devices falling within the scope of the Medical Devices Directive, 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 National Research Ethics Service (NRES) in all cases unless it can demonstrate why NRES-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 NRES guidelines. However, please note that NRES 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 Medical Devices Regulations, 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 NRES 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 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 CE marking.

4 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 (www.mhra.gov.uk).

5 Humanitarian use of non-CE-marked devices

The use of an individual non-CE-marked device falling within the scope of the Active Implantable Medical Devices Directive or the Medical Devices Directive 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.

6 Further information

The European Union has approved a harmonised standard entitled 'Clinical Investigation of Medical Devices' (ISO 14155 – parts I and II), which 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 adverse incidents of devices undergoing clinical investigation, under the provisions of the Active Implantable Medical Devices Directive and the Medical Devices Directive can be obtained from:

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7 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, material or other article, whether used alone or in combination together with any accessories or software necessary for its proper functioning, intended by the manufacturer to be used for human beings in:

- the diagnosis, prevention, monitoring, treatment or alleviation of disease or injury;
- the investigation, replacement or modification of the anatomy or of a physiological process;
- the control of conception;

and which does not achieve its principal intended action by pharmacological, chemical, immunological or metabolic means, but which may be 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 information listed below marked with a * forms part of the additional information that the manufacturer must undertake to keep available for the MHRA on request by virtue of Regulation 16(1)(b) of the Medical Devices Regulations, which incorporates Annex VIII, paragraph 3.2. If they wish, manufacturers may submit any of this additional information at the time of their initial submissions, as doing so may help the MHRA to assess a submission within a shorter period of time.

General information required

- Date of submission
- Applicant's name/address/telephone number/fax number and contact name for communication
- Whether a first submission or a re-submission
- If re-submission with regard to the same device, previous date(s) and reference number(s) of earlier submission(s)
- *If other Member States are participating in the clinical investigation as part of a multi-centre/multinational study, details of applications to other Competent Authorities in the EC
- *Details of any approval by a Notified Body of manufacturing processes at the site(s) where the device is manufactured

Details allowing device to be identified

- Generic name of device
- Model name
- Model number(s), if any

Other device details

Identification of any novel or untested features

- *Summary of experience with any similar devices manufactured by the company making the device to be tested, including length of time on the market and a review of performance related customer complaints.
- *Brief description of device and other devices designed to be used in combination with it.
- *Brief description of device, including materials in contact with the body and identification of any pharmacological components or tissues of animal/human origin.
- *A summary of the relevant or other Standards applied in full or in part, and, where Standards have not been applied, a description of the solutions adopted to satisfy the Essential Requirements specified in the Medical Devices Regulations as appropriate.
- *Instructions for use

Clinical investigation plan

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

General information

- Name(s), qualifications, address(es) of clinical investigator(s), and principal clinical investigator for a multicentre clinical investigation.
- Name(s), address(es) of the Institution(s) at which the clinical investigation will be conducted.
- Description of intended purpose of device.
- Aims and objectives of clinical investigation.
- Analysis of potential risks and benefits and how foreseeable risks will be minimized.
- Reference to important relevant scientific literature with a bibliography (if any).
- A copy of the Local Research Ethics Committee approval, whether complete or qualified.

Design

- Number of devices to be used.
- Duration of study with start and finish dates and proposed follow-up period.
- Numbers of patients to be involved.
- Whether control group is planned.
- Criteria for subject selection, inclusion, exclusion, withdrawal.
- What provisions, if any, have been made by the manufacturer for the recovery of the device (if applicable) and prevention of unauthorised use.

Data collection / analysis / statistics

- Description of methods of subject follow-up and assessment during investigation.
- Description of procedures to record and report severe adverse events and adverse device events.
- Description and justification of statistical design, method and analytical procedures.

Appendix 2 Documentation to be kept available for the MHRA

The following should not be supplied with the initial submission but is available to assessors on request:

- Full description of device, including a list of accessories, principles of operation and block or flow diagrams of major components
- Principal design drawings and circuit diagrams, including materials and biomaterials, together with a description and explanations necessary for the understanding of the said drawings and diagrams
- Description of manufacturing methods
- Detailed description of how biocompatibility and biological safety have been addressed
- Details of the method(s) of sterilization
- Description of software, logic and constraints (if relevant)
- Pre-clinical experimental data including results of design calculations and of mechanical and electrical tests and reliability checks, and any performance tests in animals.