



Medicines & Healthcare products
Regulatory Agency



Guidance on legislation

Clinical investigations of medical devices – guidance for manufacturers

January 2020

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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’

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Clinical investigation in the UK: requirements of the legislation

1. In order to be able to CE mark any device, a manufacturer must demonstrate that the stated device complies with the relevant essential requirements of the [European directives](#). 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
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.

2. 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.

3. However, 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.

4. Thus a clinical investigation of a non-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.

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-CE-marked device. Such studies should only be performed on CE-marked devices unless they form part of a study to investigate safety and performance for CE marking purposes.

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 CE-marked for the purpose being investigated.

5. Before devices intended for clinical investigation in the UK are made available to a medical practitioner for the purposes of clinical investigation, the manufacturer of the device (or their authorised representatives in the European Union) must give 60 days of prior notice to the Secretary of State for Health by writing to the UK competent authority (the MHRA). 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 (Medical Devices Regulations 2002 section 16(4), section 29(3)).

6. The legal requirements as to methodology and ethical considerations relating to clinical investigations are set out in the [Medical Devices Regulations 2002](#) (section 16 and section 29), the [Active Implantable Medical Devices Directive](#) (Annexes 6 and 7), and the [Medical Devices Directive](#) (Annexes VIII and X). 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.

7. In addition, the principles of clinical investigations of medical devices are set out in the standard [BS EN ISO 14155:2011](#) Clinical investigation of medical devices for human subjects. Good clinical practice. These are harmonised standards providing presumption of conformity with Annex 7 of the Active Implantable Medical Devices Directive and Annex X of the Medical Devices Directive.

Is a clinical investigation required: the practical decisions

8. 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 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).

9. A clinical investigation of a non-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 CE-marked or non-CE-marked, is proposed for a new purpose or function
- where in vitro and/or animal testing of the device cannot mimic the clinical situation
- where there is a new manufacturer especially of a high-risk device.

10. Notification to the MHRA will not be required if the medical device to be used is CE marked for the purpose under investigation

Clinical investigations: special circumstances

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

Clinical data may be required in the case of a device already authorized to carry the CE marking where that device is to be used for a new purpose and eventually 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.

12. Comparative studies

Notification of a clinical investigation to the MHRA is not required where a device is CE-marked for the purpose intended or, in the case of a comparative study of two devices, where each has obtained prior 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 CE-marked, the manufacturer(s) of the non-CE marked device(s) must notify the clinical investigation to the MHRA.

13. 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.

14. Clinical investigations also submitted to the FDA or other non-EU regulatory authorities

Manufacturers should clearly indicate whether the European and non-European 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 European Union, may be wider than those required by the Medical Devices Regulations, for example they may include efficacy or effectiveness. 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-EU regulatory authority will also be made to the European protocol.

15. 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 Medical Devices Regulations 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 subjects 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.

16. 'Off-label' use

If a clinician uses a 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 Medical Devices Regulations 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'.

17. 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 medical devices 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 medical devices regulations and require notification to MHRA as a clinical investigation.

MHRA strongly recommend that manufacturers contact us for guidance on whether the medical devices 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

18. Humanitarian use of non-CE marked devices

The use of individual non-CE-marked devices falling within the scope of the Medical Devices Regulations 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 CE-marked device the manufacturer and clinician must fill in a form, which is on [this web page](#).

Clinical investigations – things to consider

19. 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](#)'.

20. 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.

21. Post-market clinical follow-up

The Medical Devices Directive (Annex X) and Active Implantable Medical Devices Directive (Annex 7) 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.

22. Type of investigation

The majority of clinical investigations of medical devices under the provisions of the Medical Devices Regulations 2002 will not include a control group. The decision as to whether a control group is necessary 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 however, these should be randomised and prospective, except in exceptional and justifiable circumstances.

23. 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.

24. Labelling

All devices intended for clinical investigation must bear the wording 'exclusively for clinical investigation' (Medical Devices Directive: Annex 1, para 13.3(H) and the Active Implantable Medical Devices Directive: Annex 1, 14.1). 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 CE-marked for another purpose, explanatory labelling to this effect should be attached to the device under investigation.

25. Research ethics committee opinions

For all clinical investigations of devices falling within the scope of the Medical Devices Regulations, a relevant Research Ethics Committee (REC) opinion is required (Medical Devices Regulations 2002: Paragraph 16(3), section 29(2)). This opinion may be obtained in parallel with the MHRA notification. If the REC opinion is not provided at least 60 days prior to the intended clinical investigation, it should be forwarded to the MHRA as soon as it becomes available. No clinical investigation of a non-CE-marked device should be started until both the relevant REC opinion and the MHRA have raised no grounds for objection.

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.

26. 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 HRA.Queries@nhs.net.

Manufacturers should make it clear, when contacting the Research Ethics Service, that the investigation involves a non-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 their final decision for information purposes. The Clinical Investigation Application Form enables the manufacturer to provide authorisation allowing such communication.

27. 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 hra.queries@nhs.net. When seeking advice from the Health Research Authority you should make it clear that the investigation involves a non-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.

28. In devising its policy for the handling of clinical investigations under the provisions of the Medical Devices Directives within the UK, 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 subjects entered into the proposed clinical investigation.

29. If further information is required during the course of a clinical investigation assessment, a letter will be sent to the manufacturer requesting this information. Should the nature of the requested information be unclear, it is essential that the manufacturer contacts the MHRA as soon as possible to request clarification, or a meeting or conference call if preferred. 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.

General requirements

30. Manufacturers (or their authorised representative in the EU) are required to submit initially certain information and to undertake to make available subsequently, if requested by the MHRA, information as specified in the Medical Devices Regulations 2002: Section 16 and Section 29, the Active Implantable Medical Devices Directive Annexes 6 and 7, and the Medical Devices Directive Annexes VIII and X.

31. 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.

Initial receipt of documentation

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

33. 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.

34. 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.

35. 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 calendar days and where a notification is found to be invalid the 60 days will not commence.

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

Expert assessors

37. 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, sterilization, technology of the device, toxicology, etc.

38. 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. The MHRA will, so far as possible, bear such views in mind when appointing assessors. All assessors will be required to return to the MHRA all submitted documentation which they have received and to retain no copies. The MHRA will then return the documentation to the manufacturer, or destroy all documentation on the manufacturer's wishes, except for one copy which will be retained for record purposes.

Additional information

39. 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 (Medical Devices Regulations 2002: Section 16 and Section 29, The Active Implantable Medical Devices Directive, annexes 6 and 7, and the Medical Devices Directive, annexes VIII and X). 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. The 60 day clock will not stop whilst this requested information is being assembled.

MHRA decision

40. 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.

41. 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.

42. 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; or
- where there are reasonable grounds to suspect that the clinical investigation is not subject to controls equivalent to the requirements of the relevant European Standard (ISO 14155 parts 1 and 2); or

- where there exists expert professional opinion on the proposed clinical investigation that the risk benefit analysis given by or on behalf of the manufacturer is inaccurate and that, were the investigation to take place, there would be a significant probability of serious illness, injury 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 has delivered any documentation necessary for the assessment so late that insufficient time remains within the 60-day notification period for the MHRA to complete its assessment.

43. If the MHRA raises grounds for objection, it will notify other EU Competent Authorities and the European Commission 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 if authorisation has been given for the latter cases by the manufacturer.

44. 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 Medical Devices Regulations 2002 (SI No 618) 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 60 days, except in sections that address the original grounds for objection.

When making a resubmission please provide:

1. Any necessary documents to address the grounds for objection including red lined (showing changes being 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 60 days, 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 ;
4. A copy of the original notification documentation (with the exception of those documents revised in 1 above) for reference only.

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

46. Fees for resubmission are set out on our [website](#).

Amendments

47. 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.

48. The MHRA retains the right to request a new clinical investigation notification if the amendments are thought to increase the risk to either the patient or the user, or if the MHRA considers that the amendments constitute a new investigation in accordance with Regulation 56(3) (Medical Devices Regulations 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.

Final written report

49. Manufacturers are required to notify the MHRA when a clinical investigation comes to an end (Medical Device Regulations 2002: Section 16(11) and Section 29(10)). The MHRA may request a copy of the final written report of a clinical investigation of a device falling within the scope of the Medical Devices Directive (Medical Devices Regulations 2002: Section 16(10) and Section 29(9)). It is likely that a copy would particularly be requested under certain circumstances, e.g. where a serious adverse event has occurred associated with a CE-marked device which had undergone clinical investigation authorised by the MHRA, or where a novel technology has been investigated.

Early termination of clinical investigation

50. Manufacturers are required to notify the MHRA of the early termination of a clinical investigation and provide a justification for the early termination (Medical Device Regulations 2002: Section 16(10) and Section 29(9)). The MHRA may request a copy of the final written report of a clinical investigation of a device falling within the scope of the Medical Devices Directive (Medical Devices Regulations 2002: Section 16(10) and Section 29(9)).

Adverse events involving devices undergoing clinical investigation

51. Regulation 16(10)(a) of the Medical Devices Regulations 2002 (SI 618) and Annex X of the Medical Devices Directive 93/42 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 subject, 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 hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

52. 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 Medical Devices Directive and undergoing clinical investigation, should be reported to the MHRA (Medical Devices Directive: Annex X, Para 2.3.5 and Active Implantable Medical Devices Directive: Annex 7, Para 2.3.5). 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.

53. 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. When using the Excel template to report serious adverse events, please send the completed spreadsheet to the MHRA via email at aic@mhra.gsi.gov.uk

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

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

56. 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 (Medical Devices Regulations 2002: Section 16(7) and Section 29(6)).

Study deviations

57. Manufactures must notify the Competent Authority 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.

CE marking

58. Please inform MHRA in the event that the medical device under investigation is 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 CE mark.

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

Other MHRA guidance notes

59. 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 – guidance for pre-clinical assessors
- Clinical investigations of medical devices – statistical considerations

Any queries regarding this document or the clinical investigation procedure should be directed to devices.regulatory@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 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.

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

for the purposes of the Active Implantable Medical Devices Directive:

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;
investigation, replacement or modification of the anatomy or of a physiological process;
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.

Medical devices

for the purposes of the Medical Devices Directive:

means any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software 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 the 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.

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.

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.

Serious adverse incident

Means an adverse incident that:

- led to death;
- led to a serious deterioration in the health of the subject 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

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 Flow diagrams of how the MHRA processes clinical investigations



