MEDICAL DEVICES AGENCY
COMPETENT AUTHORITY (UK)

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EC MEDICAL DEVICES DIRECTIVES

GUIDANCE NOTES FOR MANUFACTURERS ON CLINICAL INVESTIGATIONS TO BE CARRIED OUT IN THE UK

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INTRODUCTION

1. The Active Implantable Medical Devices Regulations 1992 (SI No 3146), which implement the provisions of the Active Implantable Medical Devices Directive 90/385/EEC, and the Medical Devices Regulations 1994 (SI No 3017), which implement the provisions of the Medical Devices Directive 93/42/EEC, came into effect in the UK on 1st January 1993 and 1st January 1995 respectively. These sets of Regulations establish systems under which manufacturers must submit to the UK Competent Authority information about clinical investigations to be carried out in the UK.

2. These Notes outline the legal requirements relating to the conduct and performance of a clinical investigation as set out in these Regulations. They also provide background and guidance to manufacturers on how to apply for pre-clinical assessment of a proposed clinical investigation in human subjects, involving a device falling within the scope of either set of Regulations.

3. Manufacturers wishing to make application for pre-clinical assessment of a proposed clinical investigation 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 Medical Devices Agency of the Department of Health (referred to in this document as the UK Competent Authority), in accordance with these Guidance Notes.

4. This guidance is intended as general guidance and should not be regarded as an authoritative statement of the law nor as having any legal consequence. It follows that manufacturers and others should not rely on this guidance but should consult the legislation referred to and make their own decisions on matters affecting them in conjunction with their lawyers and other professional advisers. The Department of Health does not accept liability for any errors, omissions or other statements in the guidance whether negligent or otherwise. An authoritative statement could be given only by the courts. Information and assistance in individual cases may be sought from the UK Competent Authority whose address and telephone number are given on page 20 of this document.

BACKGROUND

5. From 1st January 1993, the provisions of the first of a series of three Medical Devices Directives regulating the safety and marketing of medical devices throughout the European Community, started to be implemented in the United Kingdom.

THE ACTIVE IMPLANTABLE MEDICAL DEVICES DIRECTIVE

6. This Directive covers all powered medical devices implanted and left in the human body, such as pacemakers, implantable defibrillators,

14. Critical analysis and evaluation of scientific literature are broad concepts which can take account of experience of an established device which is already on the market and used in clinical practice. Evaluation can also be based on relevant scientific literature, including data on the materials or type of design used in the particular device, data on the type of medical procedures used, and other non-clinical test data including animal studies.

15. However, unless safety and performance can be adequately demonstrated by other means, a specifically designed clinical investigation of a medical device is likely to be required. 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*
- *to determine any undesirable side-effects under normal conditions of use and to allow an informed clinical opinion to assess whether these are acceptable when weighed against the intended performance of the device.*

16. 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 by a clinical expert to be safe to use on a patient 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, then it would not be subject to the above requirements. Once the Directives are fully in force therefore, such studies can only be performed on CE- marked devices.

17. Clinical investigations are also required in the case of devices already authorised to carry the CE marking where the device is to be used for a new purpose. However, submission of a clinical investigation to the UK Competent Authority for assessment, 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. Where at least one or both of the devices under study is not CE-marked, and the study is designed to demonstrate compliance with the factors listed above, notification of the clinical investigation to the Competent Authority is required. It is recognised that the clinical investigation submitted may form part of a larger study which includes wider objectives than those required by the Medical Devices Regulations (This may occur particularly in the case of a multi-centre study being carried out in both North America and Europe where the requirements of the Regulatory Authorities differ).

informed clinical opinion to be acceptable when weighed against the benefits to the patient and compatible with a high level of protection of health and safety.

- *introduce controls covering the safety, performance, specification, design, manufacture, labelling and packaging of devices;*
- *specify the requirements for pre-clinical assessment of clinical investigation protocols;*
- *specify the action to be taken, if any, following a device-related adverse incident;*
- *require the Competent Authorities in each Member State of the European Union to designate Notified Bodies which are required to check and prove that relevant devices conform with the Essential Requirements by setting up and carrying out conformity assessment procedures, including auditing, quality systems and type testing.*

11. These controls are intended to ensure the safety and performance of medical devices and to prohibit the marketing of devices which might compromise the health and safety of patients, users or any relevant third party (where appropriate).

12. During the transition period, the manufacturer or importer marketing the device in the UK may choose either to follow existing national controls or to adopt the provisions of the relevant Devices Directive and implementing Regulations.

THIS TRANSITION PERIOD, HOWEVER, ONLY COVERS DEVICES PLACED ON THE MARKET AND PUT INTO SERVICE AND DOES NOT COVER DEVICES MADE AVAILABLE FOR CLINICAL INVESTIGATION.

CLINICAL INVESTIGATION IN THE UK: REQUIREMENTS OF THE REGULATIONS

13. In order to obtain the CE marking for any device, a manufacturer must demonstrate that the stated device complies with the relevant Essential Requirements. In order to demonstrate such compliance, it will sometimes be necessary to provide clinical data, which may be in one of two forms, namely:

- *either a compilation of the relevant scientific literature currently available on the intended purpose of the device and the techniques employed, together with, if appropriate, a written report containing a critical evaluation of the compilation; or*
- *the results and conclusions of a specifically designed clinical investigation.*

implantable infusion pumps, cochlear implants and implantable neuro-muscular stimulators. The Directive also includes implanted passive parts of active devices such as pacemaker leads and adaptors, and external parts that are an essential part of the systems, e.g. pacemaker programmers. Regulations implementing the Directive came into force in the United Kingdom on 1st January 1993, with a transitional period until 31st December 1994.

MEDICAL DEVICES DIRECTIVE

7. This Directive covers most other medical devices over a wide range of products from simple bandages to orthopaedic implants and high technology radiology equipment. Regulations implementing the Directive came into force in the United Kingdom on 1st January 1995, with a transitional period until 13th June 1998.

IN VITRO DIAGNOSTIC MEDICAL DEVICES DIRECTIVE

8. This proposed Directive will cover any medical device, reagent, reagent product, kit, instrument, apparatus or system which is intended to be used for the in-vitro examination of substances derived from the human body, such as blood grouping reagents, pregnancy testing and Hepatitis B test kits. It is not expected that the Regulations implementing the Directive will be required to come into force in the UK until 1998. There is no clinical investigation system for in-vitro diagnostic medical devices.

9. The main purpose of these Directives is to allow free movement of medical devices throughout the European Community, whilst at the same time ensuring device performance and safety. The Directives will replace any existing national systems in each Member State.

10. In summary, these Directives:

- *specify the medical devices to which they apply;*
- *specify the Essential Requirements which must be met before any device can be placed on the market or put into service and which are intended to ensure that:*

  (i) a device does not compromise the clinical condition or safety of the patient, the safety and health of users or, where applicable, any third party;

  (ii) a device achieves its intended purpose as designated by the manufacturer; and

  (iii) any risks associated with the use of the device are judged by

18. 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 UK Competent Authority, the risk to patients or users is increased by the proposed changes. Under these circumstances, the UK Competent Authority 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.

19. Most medical devices about to be placed on the market are likely to fall into one of three categories. Either the device is one for which previous clinical experience exists, or it is a modification of a device where the safety and performance of the modification can be demonstrated without the need for investigation in human subjects, e.g. by means of laboratory testing. For the remaining devices a specifically designed clinical investigation will be necessary in order to demonstrate device safety and performance.

20. A clinical investigation of a non-CE-marked medical device will probably be required in the following circumstances:

- *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, 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.*

21. In circumstances where it is unclear to the manufacturer whether there are sufficient existing clinical data to demonstrate compliance with the Essential Requirements in order to obtain the CE marking, discussion with the relevant Notified Body, where applicable, may prove helpful before embarking on the planning of a clinical investigation.

22. Where a clinical investigation is required, the investigation must:

- *be performed on the 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 and human subjects to reflect the aims of the investigation taking into account the potential 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 incidents and report serious incidents to the UK Competent Authority. Although this is only a requirement for those devices falling within the scope of the Medical Devices Regulations, manufacturers are encouraged similarly to report for those devices falling within the scope of the Active Implantable Medical Devices Regulations (see page 19, "Adverse Incidents of Devices Undergoing Clinical Investigation");*
- *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.*

23. The legal requirements as to methodology and ethical considerations relating to clinical investigations are set out in the Active Implantable Medical Devices Regulations: Schedule 3, and the Medical Devices Regulations: Section 16, which incorporate those parts of the relevant Medical Devices Directives which deal with clinical investigations. Additionally, the principles of the clinical investigation of medical devices are set out in the European Standard EN 540, "Clinical Investigation of Medical Devices for Human Subjects". This is a harmonised Standard providing presumption of conformity with Annex 7 of the Active Implantable Medical Devices Directive and Annex X of the Medical Devices Directive.

CLINICAL INVESTIGATIONS: IMPLEMENTATION POLICY IN THE UK

24. 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 his authorised representative in the European Union) must give 60 days prior notice to the Secretary of State

for Health by writing to the UK Competent Authority. If within that period of 60 days the UK Competent Authority has not given written notice of objection, the clinical investigation may proceed. The UK Competent Authority may give such notice of objection on the grounds relating to the health or safety of patients, users or others (Active Implantable Medical Devices Regulations: Section 7(2) and the Medical Devices Regulations: Section 16(2)).

25. By virtue of the provisions of the Medical Devices Regulations however, Member States may authorise manufacturers to commence the clinical investigation prior to the expiry of the 60 day period if the relevant Ethics Committee has issued a favourable opinion with regard to the investigation in question. This option is, however, open to the discretion of each Member State. 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 UK Competent Authority 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. The system set up for the handling of devices associated with lower risk will normally require less detailed information and all efforts will be made to handle such investigations in a shorter period of time than that required in the case of clinical investigations of devices associated with a perceived higher risk.

26. For the purposes of these Notes:

- *devices in Class I, Class IIa, Class IIb non implantable and Class IIb non long-term invasive are defined as devices associated with perceived low risks; and*
- *devices in Class IIb implantable, Class IIb long-term invasive, Class III and active implantable medical devices are defined as devices associated with perceived high risks.*

27. This categorisation has been arrived at for the purposes of efficient administration and in no way prejudices the outcome of the assessment of the proposed clinical investigation.

SPECIAL FEATURES OF CLINICAL INVESTIGATIONS

LOCAL RESEARCH ETHICS COMMITTEES

28. For all clinical investigations of devices falling within the scope of the Medical Devices Directive, a relevant Local Research Ethics Committee opinion is required (Medical Devices Regulations: Paragraph 16(1)(a) which incorporates Annex VIII, paragraph 2.2 of the Medical Devices Directive). Although not required under the provisions of the Active

Implantable Medical Devices Directive, all clinical investigations of active implantable medical devices should also receive an opinion from the relevant Local Research Ethics Committee before commencement of a clinical investigation, in accordance with current Department of Health policy and standards of professional ethics. Such opinions must be obtained from each participating centre.

29. The Local Research Ethics Committee opinion(s), whether approved or qualified, must be sent to the Competent Authority with the other required documentation when notification of a clinical investigation is made.

30. In the case of a multi-centre clinical investigation, the UK Competent Authority will carry out an assessment of that investigation, provided the opinion from one of the relevant Local Research Ethics Committees is submitted with the original documentation. In circumstances where the Competent Authority raises no grounds for objection to the investigation in question proceeding, that investigation may only commence in the institution(s) from where a Local Research Ethics Committee opinion has been obtained. The investigation may only commence in the remaining sites after the Local Research Ethics Committee approval has been received, copied to the UK Competent Authority, and a letter confirming that the investigation may proceed at the site in question has been received from the Competent Authority.

NUMBER OF DEVICES PROPOSED FOR CLINICAL INVESTIGATION

31. In assessing risks to health or safety, one of the areas that will be particularly considered by the UK Competent Authority 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 by a Notified Body. The number, therefore, should reflect the aims of the investigation, taking into account the perceived risk of the device.

CLINICAL INVESTIGATION DURATION

32. 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 manifest for a number of years and that the clinical investigation in question will only demonstrate major short term safety problems. It is intended that long-term safety problems are identified under Medical Devices Vigilance (MDV) .

TYPE OF INVESTIGATION

33. The majority of clinical investigations of medical devices under the provisions of the Active Implantable Medical Devices Regulations and the Medical Devices Regulations will not require 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.

LABELLING OF DEVICES FOR CLINICAL INVESTIGATION

34. All devices intended for clinical investigation must bear the wording "exclusively for clinical investigation" (Active Implantable Medical Devices Regulations: Schedule 2, section 14(1)(e) and Medical Devices Regulations: 2(1) and 5(1) which incorporate, inter alia, Annex I, paragraph 13.3(h) of the Medical Devices Directive). 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.

35. Medical devices intended for clinical investigation must not bear the CE marking, unless they have already been placed on the market for an intended purpose other than that under investigation.

MAKING AN APPLICATION FOR PRE-CLINICAL ASSESSMENT

HOW TO APPLY

36. Application for assessment of a proposed clinical investigation of a medical device is made by completing forms PCA1 and PCA2 and

attaching the information requested on these forms.

37. All documentation should be sent by recorded delivery.

WHERE TO APPLY

38. Application for pre-clinical assessment or any queries regarding an application should be directed to:

Medical Devices Agency,
European and Regulatory Affairs,
11th Floor Hannibal House,
Elephant and Castle,
London SE1 6TQ.

CHARGING

39. A charge will be made by the UK Competent Authority to the manufacturer for the assessment of a proposed clinical investigation as detailed in the Medical Devices Fees Regulations (SI 1995 No 2487). For details of current fee structure see enclosed leaflet. Manufacturers should note that if a notification for a clinical investigation is withdrawn within 5 days from the date of receipt by the UK Competent Authority, 50% of the relevant fee will be charged. Otherwise a full fee will be charged on withdrawal.

GENERAL REQUIREMENTS

40. Manufacturers (or their authorised representative in the Community) are required to submit initially certain information as specified in the Active Implantable Medical Devices Regulations: Schedule 4, paragraph 2(2) and the Medical Devices Regulations: 16(1)(a) which incorporates Annex VIII, paragraph 2.2 of the Medical Devices Directive, and to undertake to make available subsequently, if requested by the UK Competent Authority, further information as specified in the Active Implantable Medical Devices Regulations: Schedule 4, Section 3(1)(b) and the Medical Devices Regulations: 16(1)(b) which incorporates Annex VIII, paragraph 3.2 of the Medical Devices Directive.

41. Form PCA1 has been designed as a computer input form to help the UK Competent Authority record the applications and accompanying documentation. Form PCA2 has been designed as a reference index in order to help manufacturers ensure that all required information is available and referenced appropriately.

42. The information marked with * in this guidance document and on Forms PCA1 and PCA2 form part of the additional information which

manufacturers must undertake to keep available for the UK Competent Authority by virtue of the provisions of Schedule 4, Section 3(b) of the Active Implantable Medical Devices Regulations and Medical Devices Regulations: 16(1)(b) which incorporates Annex VIII, paragraph 3.2 of the Medical Devices Directive. If they wish, manufacturers may submit any of the additional information at the time of their initial submissions, as doing so may help the UK Competent Authority to assess a submission within a shorter period.

43. A total of eight copies of each full submission is required and must be presented with all pages in their correct numbered sequence, including reprints, diagrams, tables and other data. The method of reproduction used must allow for legible presentation of the text and any relevant drawings with their captions.

44. All information must be in English. If any part of the supporting data consists of material in another language, this must be translated. One copy of the original document in its original language should accompany the application.

DOCUMENTATION REQUIRED FOR ALL SUBMISSIONS

SIGNED STATEMENT

45. All applications must contain a statement, firstly that the device in question conforms to the Essential Requirements except with regard to those aspects of the device which are to be investigated. Where the first part of the statement is not included, an adequate justification for such an omission must be provided; and secondly, that in respect of those aspects every precaution has been taken to protect the health and safety of the patient (Active Implantable Medical Devices Regulations: Schedule 4, paragraph 2(2)(e) and Medical Devices Regulations: 16(1)(b) which incorporates Annex VIII, paragraph 2.2 of the Medical Devices Directive).

46. GENERAL INFORMATION

- *Date of submission.*
- *Applicant's name/address/telephone number/fax number and contact name for communication.*
- *Whether first submission or 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 multicentre/multinational study, details of applications to other*

Competent Authorities in the EC.

- **Details of any approval or audit by a Notified Body or other third party of manufacturing processes at the site(s) where the device is manufactured.*

47. DETAILS ALLOWING DEVICE TO BE IDENTIFIED

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

48. OTHER DEVICE DETAILS

- **Classification of device.*
- ** Brief description of device and other devices designed to be used in combination with it.*
- ** Identification of any features of design that are different from a previously similar marketed product (if relevant).*
- ** Details of any new or previously untested features of the device including where applicable, function and principles of operation.*
- ** Summary of experience with any similar devices manufactured by the company including length of time on the market and a review of performance related complaints.*
- ** Risk benefit analysis to include identification of hazards and estimated risks associated with the manufacture (including factors relating to device design, choice of materials, software) and the use of the device (CEN 1441), together with a description of what actions have been taken to minimise or eliminate the identified risk.*
- ** Description of materials coming into contact with the body, why such materials have been chosen, and which standards apply (if relevant).*
- ** Identification of any pharmacological components of device with description of intended purpose and previous experience with the use of this substance.*
- ** Identification of any tissues of animal origin incorporated within the device together with information on the sourcing and collection of the animal tissue(s) prior to manufacturing operation; and details with regard to validation of manufacturing procedures employed for the reduction or inactivation of unconventional agents.*
- ** Identification of any special manufacturing conditions required and if so how such requirements have been met.*

- ** Identification of packaging used for sterilisation of device.*
- ** A summary of the relevant standards applied in full or in part, and where standards have not been applied, descriptions of the solutions adopted to satisfy the Essential Requirements specified in the Active Implantable Medical Devices Regulations and the Medical Devices Regulations, as appropriate.*
- ** Instructions for use.*
- ** What provisions, if any, have been made by the manufacturer for the recovery of the device (if applicable) and subsequent prevention of unauthorised use.*
- ** Photograph (preferably in colour)/diagram/sample if appropriate.*

49. CLINICAL INVESTIGATION PLAN

General Information

- *Name(s), qualifications, address(es), of clinical investigator(s) and of principal clinical investigator for a multicentre clinical investigation, together with summary of necessary training and experience for use of the device in question.*
- *Name(s), address(es) of the Institution(s) in which the clinical investigation will be conducted.*
- *Description of intended purpose of device.*
- *A copy of the Local Research Ethics Committee opinion, whether fully or partially approved, or approved with conditions.*
- ** Copy of informed consent.*
- ** Reference to important relevant scientific literature (if any) with an analysis and bibliography.*

50. INVESTIGATION PARAMETERS AND DESIGN

- *Aims and objectives of clinical investigation (bearing in mind which Essential Requirements are being addressed by the Clinical Investigation in question).*
- *Type of investigation ie whether the use of a controlled group of patients is planned.*
- *Number of patients (with justification).*
- *Duration of study with start and finish dates and proposed follow-up period, (with justification).*

- *Criteria for patient selection.*
- *Inclusion and exclusion criteria.*
- *Criteria for withdrawal.*
- *Description of the generally recognised methods of diagnosis or treatment of the medical condition for which the investigational testing is being proposed.*

51. DATA COLLECTION/ANALYSIS/STATISTICS

- *Description of end points and the data recorded to achieve the end points, method of patient follow-up, assessment and monitoring during investigation.*
- *Description of procedures and details of data to record and report serious adverse events and adverse device related incidents.*
- *Description and justification of statistical design, method and analytical procedures.*

DOCUMENTATION TO BE KEPT AVAILABLE

52. 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. The following information may therefore be provided with the notification but should in all cases be available for the Competent Authority on request:

- *Full description of device, including a list of accessories, principles of operation and block or flow diagram 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. This will require an identification of the risks and hazards associated with the use of the device and how these have been addressed (see Annex) further details set out in Guidance Document No 5: Guidance on Biocompatibility Assessment, available from the Competent Authority.*
- *Details of the method(s) of sterilisation (see Annex).*
- *Description of software, logic and constraints (if relevant).*
- *Pre-clinical experimental data including results of design calculations, mechanical and electrical tests, reliability checks, and any performance tests in animals.*

INITIAL RECEIPT OF DOCUMENTATION

53. On receipt of the documentation, the UK Competent Authority will take the following action. 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 UK Competent Authority pertaining to that application.*
- *the starting date for the notification period.*

54. 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 UK Competent Authority. The sixty day assessment clock will start from the date of the formal acknowledgement of receipt of the complete notice.

EXPERT ASSESSORS

55. 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 biocompatibility, biological safety, clinical research, immunology, pharmacology, statistics, sterilisation, technology of the device, toxicology, etc.

56. Assessors from outside the Department of Health 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 UK Competent Authority. 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 UK Competent Authority will, so far as possible, bear such views in mind when appointing assessors. All assessors will be required to return to the UK Competent Authority all submitted documentation which they have received and to retain no copies. The UK Competent Authority will then return the documentation to the manufacturer or destroy all documentation, according to the manufacturer's wishes, except for one copy which will be retained for record purposes.

ADDITIONAL INFORMATION

57. Each expert assessor will be allowed 14 days in which he/she will be able to request, through the UK Competent Authority, 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 UK Competent Authority (see Active Implantable Medical Devices Regulations, Schedule 4, Paragraph 3(b) and Medical Devices Regulations: 16(1)(b) which incorporate Annex VIII, Section 3.2 of the Medical Devices Directive).

58. It is in the interests of the manufacturer to supply this additional information as soon as possible if it is requested. Failure to do so may result in rejection of the application if sufficient time does not remain within the 60 day period to complete an adequate assessment of all relevant data. The 60 day clock will not stop whilst this requested information is being assembled.

UK COMPETENT AUTHORITY DECISION

59. If, after consideration of all the evidence provided, the UK Competent Authority considers that there are no grounds relating to health or safety whereby the proposed clinical investigation should not proceed, the UK Competent Authority will notify the applicant of this decision.

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

61. Unjustifiable risks to public health or safety may exist:

- *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 (EN 540); or*
- *where there exists 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 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 UK Competent Authority to complete its assessment.*

62. 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. The reasons for objection will remain confidential between the UK Competent Authority, other European Community Regulatory Authorities and the manufacturer (or his authorised representative in the Community). They will be revealed to other persons only with the manufacturer's express consent or where there are overriding reasons involving the protection of public health and safety in accordance with Article 15 of the Active Implantable Medical Devices Directive and Article 20 of the Medical Devices Directive. An appropriate fee, as defined in the Medical Devices Fees Regulations (SI 1995 No 2487) will need to accompany the subsequent notice addressing the grounds for objection.

CHANGES OR MODIFICATIONS IN PROTOCOL

63. All changes in protocol whether relating to the device, aspects of the clinical investigation plan, investigators or investigating institutions must be notified to the Competent Authority and not implemented until a letter of agreement has been obtained from the Competent Authority.

64. The Competent Authority retains the right to request a new clinical investigation notification if the modification to the protocol is thought to increase the risk to either the patient or the user, or if the Competent Authority consider that the changes proposed constitute a new investigation.

FINAL WRITTEN REPORT

65. The UK Competent Authority 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: Section 16(5)(a)). 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 UK Competent Authority.

66. Any serious adverse incident involving a device under clinical investigation coming within the scope of the Medical Devices Directive and

undergoing clinical investigation, should be reported to the UK Competent Authority (Medical Devices Regulations: 16(1)(b) which incorporates inter alia, Annex X, paragraph 2.3.5 of the Medical Devices Directive).

ADVERSE INCIDENTS INVOLVING DEVICES UNDERGOING CLINICAL INVESTIGATION

67. The purpose of the Vigilance system under the Medical Devices Regulations is to improve the protection of health and safety of patients, users and others by reducing the likelihood of the same type of adverse incident being repeated in different places at different times. Manufacturers of active implantable medical devices undergoing clinical investigation are therefore also strongly encouraged to report adverse incidents to the UK Competent Authority, in the same way in which such incidents must be reported under the Medical Devices Regulations, within similar time constraints.

HUMANITARIAN USE OF NON-CE-MARKED DEVICES

68. The use of individual non-CE-marked devices falling within the scope of the Active Implantable Devices Regulations and the Medical Devices Regulations may be authorised by the UK Competent Authority on humanitarian grounds, provided that the UK Competent Authority 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 UK Competent Authority. The UK Competent Authority'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.

NOTES FOR CLINICAL INVESTIGATORS

69. Copies of a further short paper written especially for clinical investigators, highlighting some of the important features of clinical investigations of devices under the provisions of the Medical Device Regulations are available from:

Dr S Ludgate, Medical Director,
Room 1110, Medical Devices Agency,
Hannibal House, Elephant & Castle, London SE1 6TQ.
Tel: 0171 972 8123
Fax: 0171 972 8111

70. Any queries regarding this document or the clinical investigation procedure should be addressed to:

Dr S Ludgate (clinical aspects),
Room 1110, Medical Devices Agency,
Hannibal House, Elephant and Castle, London SE1 6TQ.
Tel: 0171 972 8123
Fax: 0171 972 8111

or:

Mr P Stonebrook (for technical and administrative matters)
European and Regulatory Affairs
11th Floor, Medical Devices Agency,
Hannibal House, Elephant and Castle, London SE1 6TQ.
Tel: 0171 972 8251
Fax: 0171 972 8112

71. 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.

72. 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.

73. ADVERSE DEVICE EVENT

means a device-related adverse event.

74. ADVERSE EVENT

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

75. 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.

76. CLINICAL INVESTIGATION PLAN

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

77. 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.

78. 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.

79. 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.

80. 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.

81. 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.

82. 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.

83. 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.

84. MULTICENTRE INVESTIGATION

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

85. PERFORMANCE OF DEVICE

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

86. 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.

87. 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.

88. SUBJECT

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

89. 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.

ANNEX

)DITIONAL NOTES ON ASPECTS OF DOCUMENTATION TO BE KEPT AVAILABLE FOR THE UK COMPETENT AUTHORITY

90. In addition to the information listed in forms PCA1 and PCA2, other documentation must be kept available for the UK Competent Authority, which may be requested for scrutiny (Active Implantable Medical Devices Regulations: Schedule 4, Section 3(1)(b) and Medical Devices Regulations: 16(1)(a) incorporating Annex VIII, Paragraph 3.2).

STERILISATION

91. If details of sterilisation are requested, the following information should be included:

- *specification of manufacturing environment used;*
- *details of any cleaning process prior to sterilisation;*
- *method of sterilisation;*
- *parameters of the sterilisation process;*
- *site(s) of sterilisation (if different from manufacturing site(s));*
- *packaging materials used;*
- *summary of sterilisation validation data;*
- *details of routine monitoring of the sterilisation process.*

MATERIALS

92. If details of materials are requested, information sufficient to characterise fully the identity and chemical composition of all materials coming into patient contact, including name and address of manufacturer, trade name/code, quantitative formulations, results of chemical analyses, assessments of the effects of sterilisation or other processes, or other data as appropriate, should be included.

RISK ASSESSMENT AND BIOLOGICAL SAFETY

93. The risk assessment should cover the rational for the decisions adopted. It should be apparent from the risk assessment, how hazards were identified and characterised and how the risks arising from the identified hazards were estimated and justified in relation to anticipated benefits. Particular attention should be paid to biological safety issues, especially for devices containing new materials that will come into contact with patients or where established materials are used in a situation involving a greater degree of patient contact. For example, where particularly

hazardous materials, may be present in the final device, the risk assessment should indicate why solutions avoiding the hazard have not been adopted. A description of how the biological safety of the device has been evaluated should be included. This should include the identity of the person(s) responsible for the risk assessment, a summary of the data examined and the basis for the judgement that the materials are suitable for the proposed use.

94. Guidance on the information appropriate for biological safety assessment is given in a separate document: Guidance Document No 5: Guidance of Biocompatibility Assessment. This is available from the UK Competent Authority.

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