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GUIDELINES ON MEDICAL DEVICES

GUIDE FOR COMPETENT AUTHORITIES IN MAKING AN ASSESSMENT OF CLINICAL INVESTIGATION NOTIFICATION

Note

The present Guidelines are part of a set of Guidelines relating to questions of application of EC-Directives on medical Devices. They are legally not binding. The Guidelines have been carefully drafted through a process of intensive consultation of the various interest parties (competent authorities, Commission services, industries, other interested parties) during which intermediate drafts were circulated and comments were taken up in the document. Therefore, this document reflects positions taken by representatives of interest parties in the medical devices sector.

MEDICAL DEVICES DIRECTIVES - CLINICAL INVESTIGATION-

GUIDELINES FOR COMPETENT AUTHORITIES IN MAKING AN ASSESSMENT OF CLINICAL INVESTIGATION NOTIFICATION

INTRODUCTION

Roles of Competent Authorities may vary between Member States in relation to assessment of clinical investigation notifications under the provisions of article 10 of Council Directive 90/385/EEC¹ and of article 15 of Council Directive 93/42/EEC², as amended.

It is important however that everybody responsible for raising “no grounds for objection” to a clinical investigation progressing ensures that the information submitted in the notification pursuant to annex 6 of Directive 90/385/EEC or annex VIII of Directive 93/42/EEC contains all the following items listed below (if appropriate) and is adequate in detail. It is equally important to note that any change to clinical investigation plan or other amendments and updates to the original document, must be equally submitted in a timely manner to the relevant Regulatory Bodies.

The information requested below is in line with the requirements of the harmonised standard EN ISO 14155.

CHECKLIST

NOTE: The following is a list of items that must be covered although the information may be provided in different documents or in different formats as required by individual Competent Authorities. Competent Authorities may also require additional documentation for their assessment needs.

1. General Information

- 1.1 Sponsor's and/or manufacturer's name and contact points for communication (similarly for authorised representative in the EU if relevant).
- 1.2 Whether first submission or resubmission.
- 1.3 If resubmission with regard to same device, previous date(s) and reference number(s) of earlier submission(s).
- 1.4 Other Member States and non European countries participating in clinical investigation as part of a multicentre/multinational study at the time of filing.
- 1.5 A signed statement (by the managing director or regulatory affairs manager or manager responsible for compliance with the essential requirements) to the effect that the device in question complies with the essential requirements except with regard to those aspects of the device which are to be investigated; and that, in respect of those aspects, every precaution has been taken to protect the health and safety of the subject.
- 1.6 Copy of the Ethics committee opinion as soon as available according to national requirements.

¹ Council Directive 90/385/EEC on the approximation of the laws of the Member States relating to active implantable medical devices, last amended by Directive 2007/47/EC of the European Parliament and of the Council.

² Council Directive 93/42/EEC concerning medical devices, last amended by Directive 2007/47/EC of the European Parliament and of the Council.

2. **INVESTIGATOR BROCHURE: Devices Identification**

- 2.1 Details allowing device to be identified
- 2.2 Trade name of device.
- 2.3 Generic name of device.
- 2.4 Model name of device.
- 2.5 Model number(s) including revision number(s), if any (or reference from apparent model number if appropriate).

3. **INVESTIGATOR BROCHURE: Other Device Details**

- 3.1 Classification.
- 3.2 Description of the intended clinical performance (ISO 14 155).
- 3.3 A description of device including a list of accessories, principles of operation and block or flow diagrams of major components, together with a brief description of other devices designed to be used in combination for purpose of the investigation, if applicable.
- 3.4 Identification of any features of design that are different from a previously similar marketed product (if relevant).
- 3.5 Details of any new or previously untested features of the device including, where applicable, function and principles of operation.
- 3.6 Summary of experience with any similar devices made by same manufacturer including length of time on market and a review of performance related problems, complaints any actions taken to address. Clinical data on device in question or similar device, if available. Reference should be made as to how experience with previous device models has affected the current iterations of design, if applicable.
- 3.7 Benefit/Risk analysis to include identification of hazards and estimated risks associated with the manufacture (including factors relating to device choice, choice of materials, software) and the use of the device, together with the description of what actions have been taken to minimise or eliminate the identified risks. (Note: may also be included in the clinical investigation plan).
- 3.8 Summary and analysis of pre-clinical testing and experimental data including results of design calculations, mechanical tests, electrical tests, tests for validation of software, reliability checks and any performance and safety tests in animals.
- 3.9 Description of materials coming into contact with the body, rationale for choice of materials and which Standards apply (if relevant).
- 3.10 Description of how biocompatibility and biological safety have been addressed including identification of the risks and hazards associated with the use the device and how these have been addressed.

- 3.11 Identification of any pharmacological components of device with description of intended purpose and previous experience with the use this substance (see attached annex).
- 3.12 Design drawings, if necessary for the understanding of the functioning of the device.
- 3.13 Description of software, logic and constraints (if relevant).
- 3.14 Method of sterilisation and validation (method, justification, if ETO-residuals) (if applicable) and methods of cleaning, disinfection and sterilisation for reusable devices.
- 3.15 Identification of any tissues of animal origin incorporated within the device together with information on the sourcing and collection of 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. This is also applicable in circumstances of genetically produced material.
- 3.16 Identification of any special manufacturing conditions required and if so, how such requirements have been met.
- 3.17 List of relevant Standards applied in full or in part, or description of solutions adapted to meet the essential requirements of the Directive if relevant standards have not been fully applied.
- 3.18 Instructions for use/labelling including risks, contra indications and warnings (if available).
- 3.19 What provisions, if any have been made by the manufacturer for the recovering of the device (if applicable, i.e. implantable devices, multiple use devices) and subsequent prevention of unauthorised use.

4. **CLINICAL INVESTIGATION PLAN (CIP): General Information**

- 4.1 Name(s), qualifications, professional positions, address(es) of clinical investigator(s), of principle clinical investigator and co-ordinating investigator (if relevant) from multicentre clinical investigation at the time of filing. **NOTE:** this can be provided separately from the CIP.
- 4.2 Name(s), address(es) of the institution(s) in which the clinical investigation(s) will be conducted; identification of the Sponsor and other institutions playing a critical role in the trial, ie centralised laboratories. **NOTE:** this can be provided separately from the CIP.
- 4.3 Name(s), address(es) of the Sponsor and Manufacturer.
- 4.4 Synopsis of the clinical investigation plan; reference to GCP standards followed, ie Declaration of Helsinki and ISO 14155.
- 4.5 A summary of necessary training experience for use of device in question, if applicable.
- 4.7 Copy of informed consent or the draft informed consent submitted in parallel to the Ethics Committee. **NOTE:** this can be a separate document
- 4.8 Copy of draft Clinical Research Form (CRF) if required. **NOTE:** this can be a separate document.

- 4.9 Rationale and justification of the clinical investigation; Summary of background to study with reference to important relevant scientific literature (if any) with analysis and bibliography; pre-clinical testing and previous clinical experience overview in support of justification for conducting the clinical investigation; device and investigation risk analysis and risk assessment.

5 **CLINICAL INVESTIGATION PLAN: Investigation Parameters and Design**

- 5.1 Objectives of clinical investigation.
- 5.2 Investigation design, eg randomised, controlled, including clear statement of the endpoints corresponding to the objectives of the clinical investigation, variables to be used, methods and timing of the assessments.
- 5.3 Numbers of subjects (with justification).
- 5.4 Duration of study with estimated start and finish dates and proposed follow up period (with justification).
- 5.5 Criteria for subject selection.
- 5.6 Criteria for withdrawal from study
- 5.7 Description and justification of hazards caused by invasive procedures that are not medically required (if applicable).
- 5.8 Description of general methods of diagnosis or treatment of the medical condition for which the investigation testing is being proposed.
- 5.9 Monitoring arrangements during the clinical investigation including request for direct access to source documents including extent of source data verification.

6 **CLINICAL INVESTIGATION PLAN: Data Collection/Analysis/Statistics**

- 6.1 Description of endpoints to demonstrate safety and performance and the data recorded to achieve the endpoints, method of subjects follow up, assessment and monitoring arrangements during investigation.
- 6.2 Description and justification of statistical design, method and analytical procedures. Statistical considerations including statistical design and methods describing how to reach endpoints to demonstrate safety and performance. Level of significance and the power of the clinical investigation, any criteria for termination of the clinical investigation (if applicable) with statistical justifications.
- 6.3 Procedures for data collection, review, cleaning, and issuing and resolving queries, if appropriate.
- 6.4 Recording and reporting procedures of clinical investigation plan deviations, if appropriate

7 CLINICAL INVESTIGATION PLAN : Safety Reporting

- 7.1 Definitions of adverse events and adverse device effects.
- 7.2 Definitions of serious adverse events and serious adverse device effects.
- 7.3 Details of procedures of those events to be reported to the relevant Ethics Committees and Competent Authority, including timelines.
- 7.4 List of foreseeable adverse events and adverse device effects, likely incidence, mitigation and/or treatment.
- 7.5 Emergency contact details for reporting serious adverse events and serious adverse device effects to the Sponsor.

8 CLINICAL INVESTIGATION PLAN : Other

- 8.1 Reference to Insurance coverage in case of injury
- 8.2 Device accountability procedures.
- 8.3 Ethics and informed consent procedures
- 8.4 Procedure for early termination or suspension of the investigation giving criteria and risk analysis.
- 8.5 Procedure for clinical investigation plan amendments
- 8.6 Final report and publication policy.

ANNEX

GUIDANCE NOTES ON MEDICAL DEVICES INCORPORATING A MEDICINAL SUBSTANCE HAVING ANCILLARY ACTION

Additional information required with regard to the medicinal substance.

- Intended purpose within the context of the device and the risk analysis.
- Source, product license (where applicable), quantity/dosage of the medicinal component, and the method by which the substance is incorporated into the device.
- Method of manufacture (solvents/reagents used in processing, residuals).
- Control of the starting materials
 - (medicinal substance specifications eg, summary of the European Drug Master File, reference to European Pharmacopoeia or national monograph of a European Member State).
 - Manufacturers may wish to cross-reference a granted Clinical Trial Exemption (CTE).
 - Please refer to “The rules governing medicinal products in the European Community” volume III, Addendum II.
- Qualitative and quantitative tests carried out on the medicinal substances.
- Stability data in relation to the expected shelf-life/lifetime of the device.
- Toxicological profile (summary of results of toxicity testing/biological compatibility).
 - This should include the effect on reproductivity, embryo/foetal and perinatal toxicity and the mutagenic/carcinogenic potential of the medicinal substance.
- Pharmacodynamics of the medicinal substance in relation to the device.
- Pharmacokinetic characteristics (local/systemic exposure patterns, duration and maximum exposure and the maximum plasma concentration peak taking into account individual variability).
 - New active substances should address the release of the substance from the device, its subsequent distribution and elimination.
- Local tolerance (particularly where the route of exposure is different to the conventional application) eg, the results of EN/ISO 10993 testing, or a review of scientific literature.

NOTE: Referral to MEDDEV 2.1.3, Section B3, which describes the documentation to be provided by the Notified Body to the Medicinal Product Competent Authority for medicinal products as part of the consultation procedure may be helpful.