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EVALUATION OF CLINICAL DATA : A GUIDE FOR MANUFACTURERS AND NOTIFIED BODIES

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.

EVALUATION OF CLINICAL DATA: A GUIDE FOR MANUFACTURERS AND NOTIFIED BODIES

1. Introduction and purpose

It is the primary purpose of this document to provide guidance to Manufacturers on reviewing and analysing clinical data and to Notified Bodies when reviewing the manufacturers evaluation of clinical data as part of the conformity assessment procedures required by 90/385/EEC (AIMD) [1] and 93/42/EEC (MDD) [2].

This document will also assist manufacturers, by providing guidance on what is expected.

2. Background

The manufacturer must demonstrate that his intended purpose(s) and claim(s) made in relation to safety and performance are achieved, as referred to in the Directives. As a general rule, such demonstration will require clinical data (Annex X, 1.1 of MDD).

Evaluation of clinical data as described in Annex X of the MDD and Annex 7 of the AIMD is particularly relevant to assessment of conformity with essential requirements given in MDD Annex I: General Requirements, sections 1 and 3 and AIMD Annex 1: General requirements, sections 1 and 2. Attention should also be paid to Annex I, I.6 (MDD) and Annex 1, I.5 (AIMD).

3. Explanation of terms

For the purpose of this document:

3.1 *Clinical data* is data which is relevant to the various aspects of the clinical safety and performance of the device. This must include data obtained from:

- (i) published and/or unpublished data on market experience of the device in question; or a similar device for which equivalence to the device in question can be demonstrated; or
- (ii) a prospective clinical investigation(s) of the device concerned; or

- (iii) results from a clinical investigation(s) or other studies reported in the scientific literature of a similar device for which equivalence to the device in question can be demonstrated.

3.2. The *Evaluation of clinical data* is the process by which clinical data from all selected sources (literature, results of clinical investigations and other) is assessed, analysed and deemed appropriate and adequate to establish conformity of the device with the pertinent essential requirements of the Directive as they relate to safety and performance, and to demonstrate that the device performs as intended by the manufacturer. The outcome of this process is a report which includes a conclusion on the acceptability of risks and side effects when weighed against the intended benefits of the device.

4. Clinical data to be provided by the manufacturer

The Active Implantable Medical Devices Directive and the Medical Devices Directive state that as a general rule, and in particular in the case of implantable devices, active implantable devices and devices in Class III, evidence of the clinical performance and safety of a medical device is provided by means of clinical data, which is supplied by the manufacturer in accordance with Annex X (MDD) or Annex 7 (AIMD). The decision as to whether clinical data is necessary however must be taken for every device on the basis of the type of data required to demonstrate compliance with the relevant Essential Requirements, the claims being made for the device in question and the risk management assessment. All the conformity assessment procedures leading to CE marking, address the issue of clinical evaluation by the manufacturer. In the case of Annexes II and III, the Notified Body is involved.

Clinical evaluation is based on the assessment of the risks and the benefits, associated with use of the device, through either:

- (i) a compilation of relevant scientific literature, that is currently available as well as, where appropriate, a written report containing a critical evaluation of this compilation (the "literature route"); or
- (ii) the results of all the clinical investigations relevant to the device in question (the "clinical investigation route"); or
- (iii) a combination of (i) and (ii) above. Where the clinical evaluation is based on such a combination, it should include an overall assessment. This assessment should take account of market experience, if available. It is important that the manufacturer relates the data to the specific device, having regard to the hazards identified (see 4.2).

The manufacturer must demonstrate whether the available data is sufficient to establish conformity with the Directive, having regard to:

- (i) the demonstration of equivalence of the device to which the data relates and the device(s) for which conformity is being assessed, and

so the applicability of the findings to the device being assessed (see section 4.3.1 (i)d)); and

- (ii) the adequacy of the data in addressing the relevant aspects of Directive conformity.

4.1. Manufacturer's statement on the clinical data used to affix the CE marking

The manufacturer should include in the technical documentation a simple statement on the clinical data used to affix the "CE" marking. The statement should make clear whether that clinical data was obtained from the published literature or the results of clinical investigations or a combination of both. Where data relates to other devices, the statement should indicate analogy with which device(s) and how equivalence was established. The full clinical data used for CE marking should be included within the technical documentation.

4.2. Identification of aspects of safety and performance to be addressed through clinical data

The manufacturer is required by the Directive to perform a risk analysis. A risk analysis is important in helping the manufacturer identify known or reasonably foreseeable hazards associated with use of the device, and decide how best to estimate the risks associated with each hazard¹. From the results of the risk analysis, the manufacturer lays out how each risk is addressed and decides on the acceptability of risks when weighed against the intended benefits.

The risk analysis includes technical and clinical aspects relating to the particular device concerned. It should distinguish between aspects associated with:

- (i) the medical procedure for which the device is intended;

eg the risks versus benefits associated with extracorporeal lithotripsy as compared with conventional (surgical and non-surgical) methods of kidney stone removal.
- (ii) the technical solutions adopted;

eg the risks versus benefits associated with different technologies of extracorporeal lithotripsy such as those involving generating shock waves with electric sparks (electrohydraulic method), with an electromagnetic generator or a piezoelectric system.
- (iii) aspects specific to the design and use of the particular device concerned;

¹ The loss/absence of the performance of a given device as claimed by the manufacturer and which could result in the loss of benefit of a treatment may be considered a hazard.

eg the risks versus benefits associated with the shock wave coupling method, size of the focal zone, the stone localisation and targeting system (X-ray, ultrasound) and the trigger method

This distinction should be used to identify the type and specificity of clinical data needed. Where the available data is not sufficient to address the identified clinical hazards relating to one or more of the above aspects, a clinical investigation(s) will be needed (see also section 4.4.1). The objectives of the clinical investigation(s) should focus on those aspects not sufficiently addressed by the available data. The manufacturer should also set out the intended benefits of the device and relate those to the accepted benefits associated with the generally acknowledged “state of the art”

4.3. Literature route

Due regard needs to be paid to the extent to which the published data are relevant and applicable to the relevant characteristics of the device under assessment and the medical procedure for which the device is intended.

A literature review should be performed by person(s) suitably qualified in the relevant field, knowledgeable in the “state of the art” and able to demonstrate objectivity.

4.3.1 Requirements

When the manufacturer's clinical evaluation to be submitted to the Notified Body takes the form of a review of the relevant scientific literature, the following requirements should be fulfilled:

(i) Methodology

a) General

A protocol for the identification, selection, collation and review of relevant studies should be written and preferably be based on recognised practice for systematic review for literature.

b) Objective

The objective of the literature review should be clearly defined. The types of studies that are relevant to the objective of the literature review should be specified, taking into account the already well established knowledge of the device.

c) Identification of data

Data should be taken from recognised scientific publications. Unpublished data should also be taken into account in order to avoid publication bias.

The literature review should state:

- the sources of data and the extent of the searches of databases or other sources of information;
- the rationale for the selection/relevance of the published literature;
- the reasons for believing that all relevant references, both favourable and unfavourable, have been identified;
- the criteria for exclusion of particular references together with a justification for this exclusion.

Note: possible data sources for a systematic literature review are for example:

- medical and paramedical databases
- technical papers from relevant Standards Committees
- foreign language literature
- “grey literature” (theses, internal reports, non peer review journals, the internet, industry files)
- references listed in primary sources
- other unpublished sources known to experts in the field (obtained by personal communication)
- raw data from published trials (obtained from personal communication)

d) Relevance of data

A literature review should clearly establish the extent to which the literature relates to the specific characteristics and features of the device under consideration.

If the published studies do not directly refer to the device in question, the following must apply.

- The manufacturer must demonstrate equivalence in all the following essential characteristics with the device, which is the subject of the published reports. Equivalence means:

Clinical:

- used for the same clinical condition or purpose;
- used at the same site in the body;
- used in similar population (including age, anatomy, physiology);

-have similar relevant critical performance according to expected clinical effect for specific intended use.

Technical:

- used under similar conditions of use;
- have similar specifications and properties eg tensile strength, viscosity, surface characteristics
- be of similar design;
- use similar deployment methods (if relevant);
- have similar principles of operation

Biological:

- use same materials in contact with the same human tissues or body fluids;

To be equivalent, the devices should have similarity with regard to the clinical, technical and biological parameters with special attention to the performance, principles of operation and materials; or if there are differences identified, an assessment and demonstration of the significance these might have on safety and performance must be set out.

For example we can consider the case where the device under consideration and the device referred to in the published studies do not have the same principles of operation ie the new device has a new principle of operation. Since a new mechanism of action does not necessarily result in a new clinical benefit, demonstration of the clinical benefit of the new device has to be generated by data resulting from a specifically designed clinical investigation since the 2 devices cannot be considered equivalent.

- The manufacturer must be able to demonstrate the adequacy of the data in addressing the aspects of conformity set out in the objective

e) Assessment of clinical data

The literature review should make clear the significance that is attached to particular references based on a number of factors. These include:

- the relevance of the author's background and expertise in relation to the particular device and/or medical procedure involved.
- whether the author's conclusions are substantiated by the available data
- whether the literature reflects the current medical practice and the generally acknowledged "state of the art " technologies.

- whether references are taken from recognised scientific publications and whether or not they have been reported in peer reviewed journals
- the extent to which the published literature is the outcome of a study/studies which have followed scientific principles in relation to design, for example, in having demonstrable and appropriate endpoints, inclusion and exclusion criteria, an appropriate and validated number of patients submitted, carried out for an appropriate duration, providing evidence and analysis of all adverse incidents, deaths, exclusions, withdrawals and subjects lost follow-up and identifying an appropriate statistical plan of analysis.

Ideally, evidence should be generated from a clinical trial (controlled if appropriate), properly designed cohort/case controlled study, well documented case histories or sequential reports conducted by appropriate experienced experts, whether in relation to the device itself or an equivalent device. If unpublished data is being included in the assessment, the literature review will need to weigh the significance that is attached to each report.

The evidence should not consist of:

- isolated case reports;
- random experience;
- reports lacking sufficient detail to permit scientific evaluation (including lack of accepted and validated statistical design if this is relevant to the design of the intended study);
- unsubstantiated opinions.

(ii) Critical evaluation of the literature

The literature review should contain a critical evaluation of the literature. This critical evaluation should:

- be written by a person suitably qualified in the relevant field, knowledgeable in the “state of the art” and able to demonstrate objectivity;
- contain a short description of the medical device, its intended functions, description of the intended purpose and application of use;
- contain an analysis of all the available data considered, both favourable and unfavourable;
- establish the extent to which the literature relates to the specific characteristics and features of the device being assessed, taking due account

of the extend of similarity between the device(s) covered by the literature and the device under assessment;

- demonstrate that those aspects of the use of the device, including performance, addressed in the clinical part of the risk analysis are met as claimed by the manufacturer, and that the device fulfils its intended purpose as a medical device;
- analyse the identified hazards, the associated risks and the appropriate safety measures of patients, medical staff and third parties involved in the study/studies, for example by reference to the manufacturer's risk analysis (see also ISO14155-2);
- contain a risk analysis relevant to the device design, materials and procedures involved, taking into account any adverse events, results of post-market surveillance studies, modifications and recalls (if known) (see also ISO14155-2);
- contain a description of the methods of weighting of different papers and the statistical methods of analysis employed taking into account the assessment methods, the type and duration of study and the heterogeneity of the population included within the study. Particular attention should be given in circumstances where there are repeated publications on the same group of patients by the same authors in order to avoid overweighting the experience;
- include an analysis of the market experience of the same or similar devices, including the results of post-marketing studies, post-market surveillance and short- and long-term adverse events;
- contain a list of publications appropriately cross-referenced in the evaluation;
- if the clinical data relates to an equivalent device, contain a statement that equivalence with all the relevant characteristics has been demonstrated;
- include a conclusion with a justification, including an assessment of any probable benefit to health from the use of the device as intended by the manufacturer, against probable risks of injury or illness from such use taking account of the "state of the art". If applicable, the findings should be compared with other studies covering the same field of application. These studies may involve other modalities, including alternative medical devices, medical therapy, surgery or other accepted health care methods provided they employ methods which are generally accepted as being common practice. The conclusions should make clear how the objectives of the literature review have been met and identify any gaps in the evidence necessary to cover all relevant aspects of safety and performance.

Note 1: conclusions should be relevant in the field of use, indications, contra-indications and instructions for use intended by the manufacturer

Note 2: the critical evaluation should be signed and dated by the author

4.3.2 Conclusions from Analysis of Literature Review

As a result of a literature review, the Notified Body needs to be able to answer the following:

- that the manufacturers' conclusions are valid;
- that the data, taken together with the available pre clinical data, is sufficient to demonstrate compliance with the essential requirements covering safety and performance of the device in question under normal conditions of use; or
- identify gaps in the demonstration of compliance with the relevant essential requirements or in the demonstration of equivalence that need addressing through the means of a specifically designed clinical investigation(s); and
- that the claims made in the device labelling are substantiated by the clinical data taken together with the pre-clinical data.

The manufacturer's report of the literature review should be written in a format that enables the Notified Body to answer the questions above.

4.4 Clinical investigations route

4.4.1. Need for clinical investigation(s)

When reviewing the manufacturer's evaluation of clinical data and whether or not a clinical investigation(s) is needed as part of this, due regard should be paid to NB-MED/2.7/R1 [5].

4.4.2. Conduct of clinical investigations

Where the results of clinical investigation(s) form part of the clinical data, the clinical investigations should comply with the relevant sections of Annex X MDD or Annex 7 AIMD. Compliance with the EN 540 [3] carries the presumption that the design, conduct and monitoring of the clinical investigation(s) conforms with the requirements of these Annexes. Whilst not carrying such a presumption of conformity, other equivalent standards may be used.²[4]

4.4.3 Requirements

² Where justified, the Notified Body may require further information to assess the manufacturers clinical investigation data.

When the manufacturer's clinical evaluation to be submitted to the Notified Body takes the form of presentation and analysis of results from a specifically designed clinical investigation(s) involving the device in question, the following requirements should be fulfilled.

(i) Identification of Relevant Documents

The following documents must be requested:

- copy of the Protocol submitted to the Competent Authority for which no grounds for objection were raised;
- copy of the letter of "no objection" from Competent Authority/Authorities (if available), together with comments made (was this a first submission to a Competent Authority? If rejected, a copy of the original "grounds for objection" should be requested);
- copy of the Ethics Committee opinion(s) and comments (was this the first submission to Ethics Committee? If previously rejected, a copy of the letter of objection should be requested);
- copy of the signed and dated final report.

(ii) Information to be checked

The following must be checked in all cases.

- **Letter of "no objection" from the Competent Authority(ies)**
- Clinical Investigation Plan (CIP): Is the CIP used for the clinical investigation the same as that submitted to the Competent Authority? Particular attention should be paid to:
 - number of patients entered
 - objectives of investigation(s) (in particular which Essential Requirements are being addressed)
 - duration of investigation(s) and patient follow up (short and long term)
 - end points in terms of diagnostic tools and patient assessment
 - inclusion and exclusion criteria;
- If parameters, especially those mentioned above, are not as set out in the original CIP, the rationale for non adherence (particularly important to note whether inclusion numbers and duration of study are cut short);
- Identification of any changes to CIP and rationale for any such changes (important to ensure Competent Authority was notified of changes, if this is relevant);
- Where the clinical investigation(s) was performed outside the EU, the manufacturer must demonstrate that the use of the device (including clinical practice and techniques) and patient population are equivalent to those for which the device will be used within the EU (if relevant).

(iii) Final Report

The contents of the Final Report should always be checked and should contain the following information

a) Summary

A structured abstract should be provided, presenting the essentials of the study, including:

- title of investigation(s);
- identification of the medical device(s), including names, models as relevant for complete identification;
- name of sponsor;
- statement indicating whether the investigation(s) was performed in accordance with CEN/ISO Standards;
- objectives;
- subjects;
- methodology;
- investigation(s) initiation and completion dates, including date of early termination, if applicable;
- results;
- conclusions;
- authors of report;
- date of report.

b) Introduction

A brief statement placing the study in the context of the development of the medical device in question and an identification of guidelines followed in the development of the Protocol.

c) Materials and methods

- device description;
- summary description of the device and its intended use, together with any modifications performed during the investigation;
- Clinical Investigation Plan summary.

d) Summary of the clinical investigation plan

This should be accompanied by any modification described. The summary should include a brief description of:

- the clinical investigation objectives;
- the investigation design;
- type of investigation;
- investigation end points;
- ethical considerations;
- subject population;
- inclusion/exclusion criteria;
- sample size;
- treatment and treatment allocation;
- investigation variables;
- concomitant medications/treatments;
- duration of follow up;
- statistical analysis including investigation hypothesis or pass/fail criteria, sample size calculation, statistical analysis methods.

e) Results

This section should contain summary information with a description of the analysis and results including:

- the investigation initiation date;
- investigation completion/suspension date;
- the disposition of patients/devices;
- the patient demographics;
- clinical investigation plan compliance;
- the analysis to include safety report, including a summary of all adverse events and adverse device events seen in the investigation, including a discussion of the severity, treatment required, resolution and assessment by the investigator of relation to treatment; performance or efficacy analysis; any sub group analysis for special population; a description of how missing data, including patients lost to follow up or withdrawn, were dealt with in the analysis.

f) Discussions and conclusions

These should contain:

- the performance and safety results of the study;
- the relationship of risks and benefits;
- clinical relevance and importance of the results, particularly in the light of other existing data and discussion of comparison with “state of the art”;
- any specific benefits or special precautions required for individual subjects or at risk groups;
- any implications for the conduct of future studies.

g) Signature

The final report should be signed off by the sponsor, the co-ordinating clinical investigator (if appointed) and principal investigator at each centre

h) Annex to the report

There should be an Annex to the report containing the following:

- clinical investigation plan, including amendments.
- list of investigators and their institutions;
- list of other parties involved;
- list of monitors;
- list of statisticians, if applicable;
- list of Ethics Committees and their approval letters.

4.4.4 Independent Analysis

An assessment and analysis carried out by an independent and unbiased expert in the field should always be considered, particularly if in-house expertise is not available.

4.4.5 Conclusions from Analysis of Clinical Investigation Data

As a result of a review and analysis of the data generated by a specifically designed clinical investigation(s), the Notified Body needs to be able to answer the following:

- that any identified pass/fail criteria of the investigation(s) have been met e.g. 98% of patient implanted with a hip prosthesis have no device related adverse events at 2 years ;
- that the results and conclusions of the clinical investigation(s) have demonstrated that compliance with the identified relevant essential requirements;
- that the claims made in the device labelling are substantiated by clinical data when taken together with the relevant pre-clinical data; and
- that the risk analysis has demonstrated that the risks associated with the use of the device as set out by the manufacturer is acceptable when balanced against the benefits to the patient.

5.0 The Role of the Notified Body

With regard to the evaluation of clinical data the Notified Body has different roles depending on the conformity assessment procedure followed.

As part of the design/type examination under Annexes II.4 or III, the Notified Body assesses the clinical data assembled by the manufacturer and the manufacturer's evaluation and the validity of the conclusions drawn. (see 5.1)

As part of quality system approval under Annex II.3, the Notified Body assesses the manufacturer's procedure for clinical data evaluation. This may include a review of examples of such evaluations. (see 5.2)

5.1. Examination of a design dossier (Annex II.4) or of a type examination dossier (Annex III)

The Notified Body (NB) examines the documentation submitted according to the preceding sections. In order to do so, the NB should possess enough knowledge and experience in clinical evaluation as stated in section 6 of this document.

5.1.1. Decision-making

In reviewing the evaluation of clinical data submitted by the manufacturer, the Notified Body decides whether or not the manufacturer has adequately:

- described and verified the intended characteristics and performances related to clinical aspects;
- performed a risk analysis and estimated the undesirable side effects;
- concluded on the basis of documented justification that the risks are acceptable when weighed against the intended benefits.

The assessment carried out by the Notified Body will typically cover the following aspects of the manufacturer's clinical data evaluation:

- the listing and characterisation of the clinical performance of the device intended by the manufacturer and the expected benefits for the patient;
- the use of the list of identified hazards to be addressed through evaluation of clinical data as described in paragraph 4.1. of this document;
- the adequate estimation of the associated risks for each identified hazard by:
 - a) characterising the severity of the hazard;
 - b) estimating and characterising the probability of occurrence of the harm (or health impairment or loss of benefit of the treatment) (document with rationale);
- the decision on the acceptability of risks in relation to each identified hazard, based on the combination of the above using the ALARP³ philosophy [6,7], and characterisation of the corresponding risk/benefit ratio as:
 - unacceptable; or
 - broadly acceptable; or

³ ALARP means "As Low As Reasonably Practicable"

- acceptable under specified conditions⁴ (see ISO/IEC Guide 51 [9]).

5.1.2. The report of the Notified Body

The Notified Body writes a report on its assessment of the submitted clinical documentation. The report may be a separate report or part of the Notified Body's overall report. In the latter case the clinical part should be clearly identified.

The Notified Body's report should include:

- identification of the manufacturer;
- identification of the medical device;
- basis of evaluation (which Directive and which Annex(es));
- submitted documents;
- description of the device;
- assessment of clinical safety and performance;
- conclusion. The NB should justify and document each step of the decision making process referred in 5.1.1. One single "unacceptable risk/benefit ratio" leads to a negative conclusion;⁵
- the names of all NB internal assessors and external experts involved in the assessment of the manufacturers documentation, together with details of the aspects assessed by each;
- date and signature of the responsible assessor(s).

5.2. Evaluation as part of quality system related procedures (Annex II.3)

5.2.1. Review of the procedures

When the manufacturer selects this procedure, the Notified Body should, as part of the review of the manufacturer's quality system, assess the establishment, maintenance and application of the manufacturer's procedures for the documented evaluation of clinical data. This should cover:

- a) the responsibility for the evaluation of the clinical data by a suitably qualified person;
- b) the identification of clinical data, both unpublished (for example contained in the manufacturers files e.g. the complaints history) and published.
- c) the relevance of the clinical data identified as demonstrating compliance with particular requirements of the Directive or cited in particular aspects of the risk analysis⁶.

⁴ The assessment of a risk/benefit ratio as "acceptable under specified conditions" implies the determination of those specified conditions under which it can be accepted. At the stage of assessment, the expected benefit to the patient, as well as the risk, has to take account of the generally acknowledged state of the art.

⁵ In some cases, the combination of the conditions specified in order to characterise different Risk/benefit ratios as acceptable may be contradictory or impracticable, and so also leads to a negative conclusion.

⁶ The record of this may take the form of relevant entries in the "ER Checklist" or the risk analysis document within the manufacturer's technical documentation (check with "Explanation of terms")

- d) assuring that clinical investigation(s) are performed in compliance with the applicable regulations and the clinical investigation plan, with a suitable justification for any deviations
- e) identification and evaluation of undesirable side effects.

This latter point involves identification of known or reasonably foreseeable hazards, qualification of their severity and of their probability of occurrence. It is part of the manufacturer's documented risk analysis based on both favourable and unfavourable data identified as relevant in order to give a balanced view.

5.2.2. Review of samples

The Notified Body, when reviewing samples of the manufacturer's clinical data evaluation, should pay special attention to the following:

- (a) whether or not the data is relevant to the device or medical procedure involved;
- (b) where the manufacturer, in the selected sample, has chosen the "literature route" (see 4.3.), whether the criteria defined in 4.3. have been applied;
- (c) where the manufacturer, in the selected sample, has selected the "clinical investigations route" (see 4.4.), whether the criteria defined in 4.4. have been applied.

When performing the assessment on samples of a manufacturer's risk/benefit assessment, the Notified Body will follow the steps indicated in 5.1.1.

6. Notified Body Specific Procedures and Expertise

Notified Bodies should establish and implement internal policies and procedures for the assessment of clinical data in order to:

- a) ensure that suitable resources, especially relevant knowledge and competence necessary for such evaluation, are available within the Notified Body and/or by contracting external experts.

Such expertise should be sufficient to identify and estimate the risks and benefits associated with the use of the medical devices. The evaluation team should be able to evaluate a risk analysis and the risk management strategy performed by the manufacturer. The evaluation team should understand the device technology as well as the medical procedure [8].

Such an evaluation may require input from a qualified medical practitioner (for example physician, dentist, nurse), as appropriate for the particular device, who has clinical experience in the pathology of the condition being treated, the usual treatment, the therapeutic alternatives etc.

When examining the results of clinical investigations, the evaluation team should have knowledge in planning, conduct and interpretation of clinical investigations. All evaluators should be trained and qualified.

Particular attention should be drawn to training of external experts with regard to the conformity assessment procedure. The Notified Body should be responsible for reviewing the opinion of these experts, taking account of their level of knowledge of the provisions of the Directives;

- b) review the evaluation of clinical data provided by the manufacturer;
- c) document the opinion with rationale of all experts involved;
- d) ensure that any external experts involved are impartial and independent from any parties involved, having due regard to any conflict of interest which may compromise impartiality (see also MedDev 2.10/2 [11]);
- e) document the result of their assessment. This is achieved through a specific report which may be part of, or may be referenced, in the overall design / type examination report;
- f) preserve confidentiality of the information and data received from the manufacturer, especially within the terms for contracting external experts.

7. References

1. Council Directive 90/385/EEC of 20 June 1990 concerning active implantable medical devices
2. Council Directive 93/42/EEC of 14 June 1993 concerning medical devices
3. EN 540: Clinical investigation of medical devices for human subjects, 1993
4. ISO 14155 Clinical investigation of medical devices
5. Guidance on when a clinical investigation is needed for CE marking, NB-MED/2.7/Rec1
6. Task force on CE marking of existing products, NBM/026/95 rev 2.
7. EN 60601-1-4: Medical electrical equipment Part 1: General requirements for safety, 4. Collateral Standard: Programmable electrical medical systems
8. Committee draft ISO/CD 14971, Medical Devices - Risk Management Dated 1998-05-21.
9. MedDev 1/94 Rev 10: Guidelines for Regulatory Auditing of Quality Systems of Medical Device Manufacturers.
10. ISO/IEC Guide 51 Guideline for the inclusion of safety aspects in Standards
11. MedDev 2.10/2 Rev 01.03.99: Designation and monitoring of Notified Bodies within the framework of EC Directives on medical devices.