

March 2010 – Clinical Data Requirements in the Era of Directive 2007/47/EC

In spring 2010, there will be two documents manifesting the requirements with regard to clinical data for the certification of medical devices: the Directive 2007/47/EC as well as the MEDDEV 2.7.1 Rev. 3.

This Med-Info may be used as an introduction to the structure and some essential details regarding the requirements for clinical data, but it does not obviate the need for review of the original documents.

Directive 2007/47/EC

With regard to the requirements for clinical data, 2007/47/EC now includes a variety of details – in contrast to the original 93/42/EEC Directive. Although the relevant contents are not really new, this Directive:

- provides a definition of clinical data, which is understood as *“safety and/or performance information that is generated from the use of a device”*; in order to generate adequate data, these may be taken from clinical investigations, scientific literature, or other clinical experience with equivalent devices
 - makes a clinical evaluation for any medical device mandatory; such an evaluation must follow *“a defined and methodologically sound procedure”*. Furthermore, the clinical evaluation shall be documented. An additional explicit requirement in that context is an active update of the performed clinical evaluation with data from post-market experience
 - postulates a positive risk-to-benefit ratio based on clinical data
- sets out different clear conditions in case the literature route is followed:
 - a) The evaluation of the relevant scientific literature must include a total of four different aspects, i.e. safety, performance, design characteristics as well as intended purpose of the device, which means that this route will only be feasible if it covers adequate information for all of these different aspects
 - b) Equivalence of all data taken for demonstration of the essential requirements must be demonstrated
 - c) In addition, the evaluation must be performed *“critically”*
 - requires due substantiation to base the demonstration of essential requirements for any device on *“performance evaluation, bench testing and pre-clinical evaluation alone”*
 - includes different explicit requirements in case the clinical trial route is followed:
 - a) The results of all investigations made are to be evaluated *“critically”*
 - b) Clinical investigations are to be performed *“unless it is duly justified to rely on existing clinical data”* for implantable devices and class III devices
 - c) Different specific requirements are dealing with the procedure of a clinical trial, including reporting of serious adverse events and end of a study, communication requirements in case a clinical trial is refused/halted by a Member State, or modification is requested; besides, the documents to be provided for a clinical investigation are set out

- requires due justification where post-market clinical follow-up as part of the post-market surveillance plan is not deemed necessary
- postulates an adequate justification in case clinical data are not deemed necessary, based on risk management output, under consideration of the specifics of the device/body interaction, the clinical performances intended, and the claims set out. In that, such a process should also be documented adequately; eventually this again implies a clinical evaluation
- provides a modification of classification of medical devices, i.e. a new definition of central circulatory system

For details, reference is made to Article 1, Article 15, Annex VIII, Annex X and Annex XI of the Directive.

MEDDEV 2.7.1 Rev. 3

The new MEDDEV 2.7.1 Rev. 3 regarding clinical evaluation should be regarded to be more than just an update of the previous revision, as it now additionally includes almost the full GHTF SG5/N1R8 "Clinical Evaluation" guideline as well as an extensive clinical evaluation checklist for Notified Bodies.

The following sections will not list the entire content of the MEDDEV paper, but will rather focus on aspects which are either new, or anticipated to result in issues for different processes. Additionally, basic information regarding general requirements may be taken from our earlier Med-Info "Requirements for Clinical Data" (August 2007).

The preface of MEDDEV 2.7.1 Rev. 3 points out that it is not legally binding; nevertheless *"it is anticipated that the guidelines will be followed within the Member States"*. An alternative approach has to be duly justified in either case. Therefore, a sound rationale should be part of the documentation.

Objectives of the clinical evaluation

The clinical evaluation for any medical device shall demonstrate

- clinical safety and
- clinical performance according to its intended use and
- positive overall risk-to-benefit ratio which must be based on current state-of-the-art.

Mode of the clinical evaluation

Clinical evaluation has to be understood as an *"ongoing process throughout the life cycle of a medical device"* which is documented by the clinical evaluation report (CER). It has to be *"repeated periodically as new clinical safety and performance information about the device is obtained during its use"*, i.e. any new clinically relevant information from, for example, scientific literature or post-market experience which is not included in an existing clinical evaluation must induce an update of the original evaluation. Furthermore, the manufacturer has to ensure that a check for any necessary updates is performed regularly and in due time.

Any clinical evaluation shall be *"thorough and objective [...] demonstrating valid clinical evidence"* which is to be understood as following basic scientific principles considering both favorable and unfavorable data, and is made transparent to enable an independent review.

As a general principle, any data allowing the clinical assessment of specific issues as set out in the beginning of the clinical evaluation process can (and should) be used; at the same time, it is regarded as essential to critically assess validity as well as transferability of any such data separately.

Qualification of authors

The MEDDEV provides requirements regarding the qualification of the author(s) of a CER. Although not listing required formal professional qualifications, it is clearly outlined that

exclusively “a suitably qualified individual or individuals”, being able to demonstrate knowledge of

- a) device technology and its application as well as
- b) “diagnosis and management of the conditions intended to be treated or diagnosed by the device” as well as
- c) research methodology including clinical investigation design and biostatistics, are regarded as adequate.

Regarding the requirements for literature review, it is required that this review has to be “developed and executed by persons with expertise in information retrieval”.

This clearly outlines that not necessarily one single author may have to be responsible for the complete clinical evaluation. If the expertise of different experts is regarded necessary, this should be outlined in the CER.

Components of clinical data

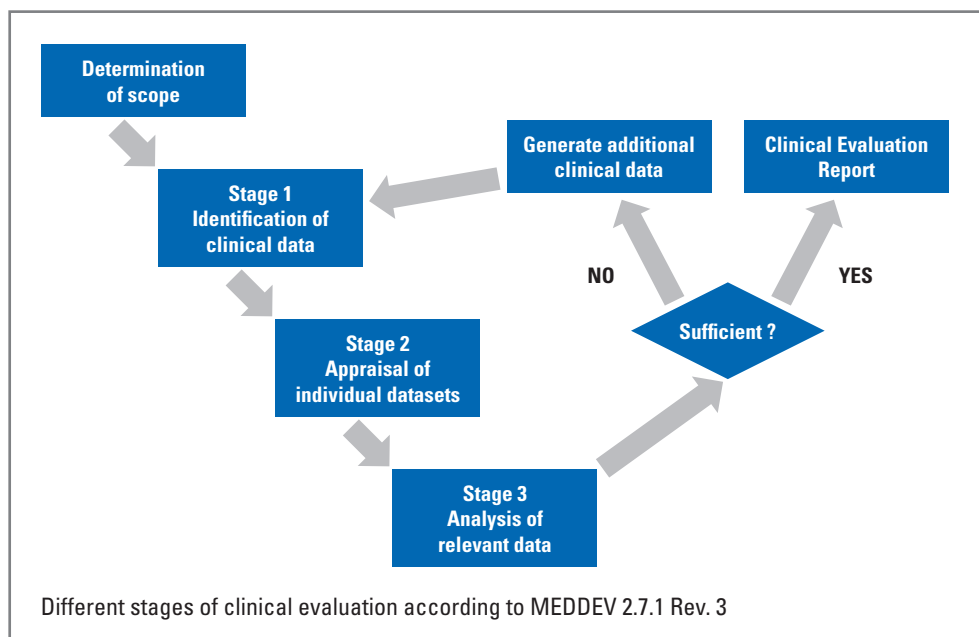
In general, the clinical evidence for a medical device may consist of:

- no clinical data for which adequate justification for any of the aspects set out above must be provided; in addition, reference to the pertinent sections of the risk analysis shall be made
- demonstration of conformity to harmonized performance standards: This may be regarded as adequate for devices based on well-known, long-standing technology for which no additional or altered clinically relevant risk based on the design or medical use is to be anticipated, when compared to established products
 - scientific literature
 - bench testing
 - animal studies
 - clinical experience
 - clinical studies
- OR a combination of different components as listed above

Note:

- It should be taken into account that in all cases where no clinical study is performed, this has to be “duly substantiated”.

Stages of Clinical Evaluation



In principle, such a strategy is neither new for the demonstration of compliance with the Directive nor different from a basic scientific approach, i.e. the process of systematically finding and critically appraising information relevant for the assessment of a product regarding its risk-to-benefit ratio.

Scope of clinical evaluation

First of all, any items of a new device relevant from a clinical perspective, i.e. design features, intended purpose, specific claims and clinically relevant risks, shall be defined prior to starting the evaluation. At the same time, *“the manufacturer will need to give consideration to the advantages and limitations of each data type”*. It is important to note that a description and assessment of any clinically relevant risk is crucial to be included in the CER; a pure cross-reference to the formal risk analysis cannot be regarded as adequate.

Identification of data

a) Literature review

An important, inevitable step for any route chosen to demonstrate the essential requirements of a medical device is a literature review which has to be documented by:

- search protocol: This document to be compiled prior to starting the review includes e.g. sources of data and justification, the extent of any search to be performed, selection criteria for papers and justification, and strategies to avoid duplicates
- the search report: It provides results of the performed literature search and shall contain a detailed description of the screening and selection performed during literature search, criteria for exclusion of particular references (+ justification), and reasons for believing that all relevant references, both favorable and unfavorable ones, have been included
- copies of the literature taken into consideration

Suitable literature shall be relevant for the device under assessment regarding device design and clinical use. Besides, the literature review must be up-to-date, i.e. include any recent relevant publication.

In a second step, each single selected publication must be evaluated separately with regard to the relevance of the author's background and expertise, whether his or her conclusions are substantiated by the available data, whether the publications reflect current state-of-the-art, whether references are taken from recognized scientific publications, and whether the study forming the basis for the publication was performed according to scientific principles. Naturally, this requirement will not be easy to address in some cases; in case of doubt it is therefore recommended to include the publication.

Notes

- A formal literature search is also to be performed in case the clinical trial route is followed (for details, see EN ISO 14155).
- All documents listed above, i.e. search protocol and search report, are to be attached to the CER.
- Abstracts of scientific publications provide a first impression, but at the same time they do not allow a critical review. Therefore, a pure abstract search cannot be regarded to fulfill the requirements of a literature review. Besides, copies of the full publications rather than copies of abstracts are to be attached to the CER.

b) Bench testing, pre-clinical testing

As outlined above, it has to be demonstrated for an individual case that bench testing and/or pre-clinical testing can be regarded as sufficient to demonstrate compliance with the essential requirements. This should also take into account the risk analysis and device/body interaction.

Notes

- In any case, if such testing is used, e.g. an adequate sample size is regarded as crucial to provide validity of results; this should be done by formal sample size estimation. Pure reference to long-standing practice cannot be regarded as adequate.
- The relevant test protocols and test reports shall be attached to the CER.
- Due diligence should be used to choose models or tests adequate for the pertinent clinical issue; in addition, evaluation of the degree of transferability of such testing results to clinical use of the device is prerequisite for the use of any such data.

c) Clinical experience

Clinical experience may also be used to demonstrate compliance with the essential requirements; this is understood as clinical use of the device outside clinical investigations, and may pertain clinical data either of the device in question or an equivalent device. Examples for such clinical experience include post-market surveillance reports, registries, cohort studies, clinically relevant field corrective actions, etc.

It should be considered that availability of sufficient information for an objective assessment is essential, which at the same time will be the major obstacle of such databases. Furthermore, it should be noted that anecdotal reports or expert opinions are not regarded as adequate sources of relevant information for the clinical assessment.

d) Clinical investigation

A clinical investigation to be considered for demonstration of the compliance with the essential requirements:

- shall be performed according to EN ISO 14155/ comparable standard as well as Annex 7 (AIMD)/Annex X (MDD)

- shall be in compliance with local regulations
- shall include the following documents: Clinical Investigation Plan (CIP, including amendments and rationale), Ethics Committee(s) documentation, informed consent forms/patient information documents, case report forms, monitoring and auditing records, Regulatory Authority Approvals and correspondence, signed and dated final report. A justification for the chosen clinical investigation route must also be available.

If any of the above listed items is not applicable, this shall be stated and justified.

An adequate final study report includes different sections such as a summary of plan and results (synopsis), introduction, materials and methods, results, discussion and overall conclusions, list of abbreviations and definitions, signatures of the sponsor and the principal investigator, a list of investigators/institutions, lists of monitors, statisticians and Ethics Committees, and tabulation of all relevant datasets including CIP deviations, adverse events and withdrawals/discontinuations.

The CER shall assess whether the investigation was conducted as planned; in case there were deviations from the original plan, its impact on the veracity of data must be evaluated.

Furthermore, the CER must assess inferences from the investigation regarding performance and safety. Issues to be addressed by the CER include:

- whether any identified pass/fail criteria were met by the trial
- whether performance and safety were demonstrated by the results and conclusions of the trial
- whether any labeling claim is substantiated by clinical data

This clearly indicates that a final report of a clinical study will in no case replace the CER. An adequate clinical study may be performed outside Europe; at the same time, equivalence to the requirements as set out above shall be demonstrated.

The sample size shall be adequate to clearly demonstrate, rather than to suggest clinical safety and performance of the device under assessment.

The chosen study objectives must address the open issues to be assessed by the clinical evaluation.

Notes

- Routinely, a typical feasibility trial will rarely fulfill relevant requirements; in addition, missing control groups or inadequate follow-up may hinder the demonstration of safety and performance of a medical device
- Design/labeling differences of a device used in the clinical study, and the final device calling for certification may cause major obstacles.
- According to common experience, a clinical trial without any protocol deviation is extremely rare; therefore, missing documented protocol deviations routinely point at documentation issues.
- Any interim analysis of an ongoing clinical trial requires corresponding provisions set out in the CIP in advance.
- Transferability of results of a well-designed homogenous clinical trial to real-world conditions of a marketed medical device shall be evaluated in detail.

Appraisal of clinical data

Appraisal of each data gained is the next step, evaluating benefits and limitations. Its goal is to determine its suitability to address the questions about the device set out in the beginning, and its contribution to demonstrate clinical safety and performance of the device.

It is regarded as important that

- the appropriate criteria for appraisal were identified in advance, i.e. prior to starting the evaluation process;
- a justification for the chosen appraisal criteria is given;
- the approach of appraisal is performed in a consistent manner.

Sufficient information in the datasets to enable a *“rational and objective assessment of the information and make a conclusion about its significance”* is essential for this step. To enable such an evaluation, the methods used to generate and collect the data must be examined, as well as *“the extent to which the observed effect ... can be considered to be due to intervention with the device”*.

It should be taken into consideration that there is no single, well-established method for appraisal which may be used in any case; depending on the risk level and the novelty of technology, different appraisal approaches may be adequate.

Note

It should be taken into consideration that the risk level as outlined above is not necessarily identical with the risk class of the device according to the Directive(s); it rather depends on the risks evaluated at the beginning of the process, and the information available to assess the risks.

Criteria for appraisal of literature

Suitability criteria are e.g. whether

- the data were generated from the device in question;
- the device was used for the same intended use as the device under assessment;
- the data was generated from a patient group representative for the intended population;
- there is sufficient information for a rational and objective assessment included in the data available.

Appraisal criteria for data contribution e.g. include whether

- the study design was appropriate;
- the intended performance is reflected by reported outcome measures;
- the duration of the follow-up was long enough to assess treatment effects and identify complications;
- a statistical analysis was provided and if it was appropriate, and whether the treatment effect observed was clinically significant.

In that context, differences in the validity of published results based on the methodology chosen should be considered and weighed accordingly. MEDDEV 2.7.1 Rev. 3 provides appraisal criteria examples for different types of clinical studies such as randomized controlled trials, cohort studies, case-control studies and case series.

In conclusion, the appraisal step evaluates the validity of the sources used, the suitability of the results, and the applicability of the results to the issues raised.

Analysis of clinical data

Purpose of this step is to determine whether the appraised datasets available demonstrate the clinical safety and performance of the device under assessment.

The tasks are to explore the results of the pivotal datasets, and to evaluate consistency of results across particular device performance characteristics and identified risks by taking into consideration all datasets.

This will then allow the decision whether

- the device performs as intended;
- there are no undue safety concerns;
- the clinical risk-to-benefit ratio is positive.

Naturally, this will only be possible by taking into consideration the current state-of-the-art.

The result of that stage will be either that sufficient data is available, enabling the risk-to-benefit assessment, or that additional data will have to be generated.

Notes

- In case the equivalence approach is chosen, i.e. by using literature, demonstration of clinical and biological and technical equivalence of the device used in literature and the device under assessment is inevitable; if there are any differences, the significance of any such difference must be evaluated.
- Also, as already outlined above, in case of pre-clinical testing transferability of data to a clinical setting according to the claimed Intended Use must be demonstrated.

CER

The Clinical Evaluation Report shall include all the documented results of the clinical evaluation as indicated above. It finally must outline:

- scope and context of the evaluation
- justification for the chosen route
- all clinical data evaluated, including the extent to which the literature quoted relates to the characteristics and features of the device under assessment
- any appraisal and analysis stage
- any conclusion made

In that context, it is regarded as essential that the CER can be read as a stand-alone document evaluable by an independent party.

The CER must be *“approved by an expert knowledgeable in the ‘state of the art’ and able to demonstrate objectivity”*; the documentation of approval has to be included.



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The CER shall include:

- device description including formal intended use, indications and contraindications; this information must be in compliance with the instructions for use
- an analysis of all identified risks and safety measures
- any relevant experience from prior clinical use of the device; in case similar devices were used, post-market experience should also be documented and assessed in the CER
- description of weighting methods of different papers and statistical methods of analysis
- signature by the author and date

A possible format for a CER is included in the MEDDEV.

Items to be checked by the Notified Body

MEDDEV 2.7.1 Rev. 3 includes a detailed checklist for the assessment of the clinical evidence by the Notified Body. In order to ensure an adequate documentation, these issues should be considered already for the compilation of clinical data.

Essential items include whether

- the overall assessment has been performed in a systematic, thorough, critical and objective manner;
- a critical and objective assessment of the different datasets used to demonstrate clinical safety and performance is available
- any clinically relevant risk is identified, adequately estimated (severity and probability), and addressed by clinical data; in addition, whether all clinical risks are included correspondingly in the labeling (IFU);
- any labeling claim regarding safety and performance is substantiated by the available clinical data;
- the conclusions drawn in the documentation can be regarded as valid;
- the risk-to-benefit ratio is finally positive with regard to the current state-of-the-art
- an appropriate plan for Post Market Clinical Follow-up (PMCF) is available; in case no PMCF plan is available, an adequate justification is necessary;
- adequate post-market surveillance is in place;
- there is commitment to inform the Notified Body of significant updates to clinical evaluation based on post-market experience or scientific publications;
- any deviation of performed steps from requirements as outlined in MEDDEV 2.7.1 Rev 3. is justified.

Your contact partner at TÜV SÜD Product Service can give you further information:

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