



applicable for  AIMDD,  MDD, and  IVDD

**CL 2010-1**

## **Checklist for audit of Notified Body's review of Clinical Data/Clinical Evaluation**

### **Introduction**

Notified Body (NB) assessment of clinical data/clinical evaluations is an essential part of the conformity assessment procedure, especially for class III and implantable medical devices. Regarding class IIa and IIb devices, clinical evaluations should be assessed as part of the representative sampling and assessment of technical documentation in line with NBOG BPG 2009-4 [1]. The NB should review a sample of manufacturer's technical files/recent design projects to ensure compliance with manufacturer's procedures for the evaluation of clinical data. In addition, an in depth review of items sampled on a representative basis should be undertaken to verify the validity of the data presented and to ensure the adequacy of the manufacturer's procedures.

It is critical to note that Annex I.6a of 93/42/EEC as amended requires that demonstration of conformity with the essential requirements must include a clinical evaluation in accordance with Annex X unless adequate justification for exclusion based on risk management output and in the context of the device/body interaction, the clinical performances intended and the claims of the manufacturer. Adequacy of demonstration of conformity with the essential requirements by performance evaluation, bench testing and pre-clinical evaluation alone has to be duly substantiated.

### **Scope of document**

This document is intended to act as a checklist for designating authorities when performing assessments of a NB to address the NB's capability for assessments of clinical evaluation documents and assessment of specific clinical data presented in support of conformity.

This document is in keeping with the structure of other related guidance on NB monitoring on the basis of general requirements, quality system requirements, resource requirements and process requirements for the NB. However, as there are no specific additional requirements under either the general or quality system requirements for a NB in relation to clinical evaluation the document is divided into two main sections:

- A Resource Requirements
- B Process Requirements

<b>A</b>	<b>Resource requirements</b>	
<b>A1</b>	<b>Qualification criteria</b>	
A1.1	Does the NB define criteria for competence and training requirements for NB auditors/reviewers/subcontractors/experts evaluating clinical data as detailed under section 10.3 of MEDDEV 2.7/1 [2]?	
A1.2	Does the NB have a process documented as to how these criteria and training requirements are authorised and recorded?	
A1.3	Does the NB have a process and evaluate the competency of auditors/reviewers on a regular basis?	
<b>A2</b>	<b>Competence</b>	
A2.1	Does the NB possess relevant regulatory knowledge and clinical competence necessary for such evaluation?	
A2.2	Does the NB possess sufficient expertise to identify and estimate the risks and benefits associated with the use of the medical devices and to appropriately evaluate a risk analysis/risk management strategy?	
A2.3	Does the NB possess relevant regulatory knowledge and clinical competence necessary for such evaluation?	
A2.4	Does the NB team should possess sufficient knowledge of the device technology and the medical procedure?	
A2.5	Does the NB team have input from qualified medical practitioners with clinical experience in the pathology of the condition being treated, the usual treatment and alternative treatments?	

A2.6	In relation to clinical investigation data, does the NB team have knowledge in planning, conduct and interpretation of clinical investigations?	
A2.7	Are auditors/reviewers required to declare whether an assessment is outside of their competence?	
A2.8	Does the NB require that teams undertaking quality system audits include individuals competent in the examination of clinical data?	
A2.9	Does the NB require all individuals undertaking assessments of clinical parts of the technical documentation to be qualified to exam clinical data?	
<b>A3</b>	<b>Training</b>	
A3.1	Are NB auditors/reviewers specifically trained in the documents outlined in section B2?	
A3.2	Does the NB have a documented process for training and providing guidance for external experts on conformity assessment procedure(s), provisions of the relevant Directive, relevant guidance documents, relevant standards and the context of the assessment they are providing?	
A3.3	Does the NB have a process requirement for documenting the training of auditors/reviewers/external experts?	
<b>A4</b>	<b>Subcontractors/external experts</b>	
A4.1	Does the NB utilise external experts for the assessment of technical (clinical) documentation?	

A4.2	Does the NB have a process documented for ensuring that external experts used by the NB are impartial and independent from any parties involved, having due regard to any conflict of interest?	
A4.3	Does the NB process ensure that the confidentiality of the information and data received from the manufacturer is maintained by contracting external experts?	
A4.4	Does the process referenced in A4.2 necessitate that the NB specifically document how any specific potential conflicts have been satisfactorily resolved?	
A4.5	Does the NB incorporate review reports from external experts into their assessment report?	
A4.6	Does the NB ensure that any queries or recommendations arising from the external expert review are appropriately followed up on?	

B	Process requirements	
B1	Does the NB have a procedure for the examination of clinical data under the relevant conformity assessment Annexes?	
B2	Does the NB procedure for examination of clinical data take account of: <ul style="list-style-type: none"> <li>(a) Annex X of 93/42/EEC/ Annex VII of 90/385/EEC as amended</li> <li>(b) MEDDEV 2.7/1 [2]</li> <li>(c) MEDDEV 2.7/2 [3]</li> <li>(d) EN ISO 14155-1/2 [4]</li> <li>(e) MEDDEV 2.12/2 [5]</li> <li>(f) Relevant harmonised standards</li> <li>(g) Relevant GHTF documents</li> </ul>	

<b>B3</b>	<b>NB assessment during quality system audit</b>	These process steps should be included during assessment during quality system audit and audit during specific assessment of technical (clinical) documentation.
B3.1	Does the NB confirm that the manufacturer has a documented process for:	
B3.1.1	Compiling a clinical evaluation in accordance with 93/42/EEC Annex X/90/385/EEC Annex 7 and MEDDEV 2.7/1 and 2.7/2 (if appropriate)?	
B3.1.2	Conducting clinical investigations in accordance with 93/42/EEC Article 15, Annex X and EN ISO 14155-1/2?	
B3.2	Does the NB check that the manufacturer has a process to define and verify the competence of personnel conducting: (a) Clinical literature searches (b) Clinical evaluations (c) Clinical investigations	
B3.3	Does the NB request details of any ongoing, terminated and completed clinical investigations, including samples of final reports during surveillance audits of manufacturers?	
B3.4	Does the NB check for details of notifications of clinical investigations to relevant Competent Authorities (CAs) and Ethics Committees including letters of objection/no objection with comments and verify that clinical investigations have undergone appropriate regulatory and ethics review?  Does the NB check that the investigation notified is consistent, in terms of design and endpoints with the investigational results presented?	

B3.5	Does the NB check whether the sponsor has fulfilled any conditions before starting the clinical investigation?	
B3.6	Does the NB check that serious adverse events occurring during clinical investigations have been reported to the appropriate regulatory/ethics authorities in line with requirements of the relevant Directive?	
B3.7	Does the NB review the follow up of patients/post market surveillance activities for clinical investigations that have been terminated (particularly for early terminations)?	
B3.8	Does the NB check that any deviations from the investigational protocol have been appropriately followed up and notified to the relevant ethics and regulatory authorities?	
B3.9	For ongoing clinical investigations: Does the NB check that the investigator's brochure has been updated with the necessary information based on safety data?	
B3.10	Does the NB check that in circumstances where an investigation has been discontinued prematurely that a valid justification has been provided and that the results of the investigation have been appropriately included in the evaluation?	
B3.11	Does the NB check during quality system audit that the manufacturer has a procedure in place to gather data from clinical experience to update their clinical evaluation of the device on an ongoing basis?	
B3.12	Does the NB check during quality system audit that the manufacturer has systems and processes in place in order to collect data from clinical experience including: (a) post-market surveillance systems	

	<ul style="list-style-type: none"> <li>(b) post-market clinical follow up plans in line with the relevant Directive and MEDDEV 2.12-2 [5]</li> <li>(c) adverse event databases from clinical investigations</li> <li>(d) vigilance systems in accordance with the relevant Directive and MEDDEV 2.12-1 [6]</li> <li>(e) systems for gathering data from compassionate use applications</li> <li>(f) clinical experience from similar devices</li> </ul>	
B3.13	<p>Does the NB process check that the manufacturer has a procedure to update the clinical evaluation on an ongoing basis as data emerges from clinical investigations, post-market surveillance, post-market clinical follow-up, market experience etc.</p>	



<b>B4</b>	<b>NB Assessment of technical documentation on clinical evaluation</b>	
B4.1	Does the NB conduct assessment of technical (clinical) documentation during site assessment?	
B4.2	If the NB conducts on-site assessment of technical (clinical) documentation: Are the NB audit teams appropriately competent to do so?	
B4.3	Does the NB procedure assess the manufacturer's selection of and justification for personnel conducting the evaluation based on:	
B4.3.1	Qualifications and documented experience?	
B4.3.2	Knowledge of the device technology and its application?	
B4.3.3	Knowledge of research methodology (clinical investigation design and biostatistics)?	
B4.3.4	Diagnosis and management of the conditions intended to be treated or diagnosed by the device?	
B4.4	Does the NB:	
B4.4.1	Assess the manufacturer's evaluation and verify the validity of the conclusions drawn?	
B4.4.2	Verify the performance characteristics of the device under the normal conditions of use?	
B4.4.3	Verify that the clinical data presented in the clinical evaluation is sufficient to meet each relevant Essential Requirements of the relevant Directive?	
B4.4.4	Verify that there is a list of identified hazards to be addressed, an adequate estimation of associated risks for	

	each identified hazard and a decision on the acceptability of the risks for each hazard?	
B4.4.5	Verify that the risk-benefit analysis of the device under the normal conditions of use (to take account of other 'state of the art' devices, technologies and procedures) has demonstrated that the risks are acceptable when balanced against benefits to the patient?	
B4.4.6	Ensure that the claims made in the device labelling are substantiated by clinical data?	
B4.5	Where manufacturers have deemed that clinical data is not deemed necessary to demonstrate conformity with the Essential Requirements of the relevant Directive:	
B4.5.1	Does the NB check that this has been adequately justified? Has the NB documented their conclusion on the validity of this decision?	
B4.5.2	Does the NB assess that the manufacturer's decision is justified in the context of the output of the risk management process, the device body interaction and the claims made for the device?	
B4.5.3	Does the NB assess whether the performance evaluation, bench testing and pre-clinical evaluation alone are adequate to demonstrate conformity?	
B5	Where manufacturers have deemed that a specific clinical investigation is not required for implantable or class III medical devices does the NB check that an adequate justification has been made to rely on existing/available clinical data? Has the NB commented on the validity of the manufacturer's decision?	

B6	Does this procedure address that the clinical data (literature or investigation) when taken together with the available pre-clinical data is sufficient to demonstrate compliance with the Essential Requirements covering safety and performance of the device under normal conditions of use? Does the NB specifically document this?	
B7	Does the NB procedure check that the manufacturer has identified the pertinent standards to the device under assessment?	
B8	Does the NB request reports on post-market surveillance/post-market clinical follow-up data from the manufacturer for specific products (e.g. when identification of emerging risks/evaluation of long term safety and performance is critical)?	
<b>B9</b>	<b>NB Assessment of data from Scientific Literature</b>	
B9.1	Does the NB procedure require submission and assessment of the: (a) literature search protocol (b) literature search report (c) full copies of published articles identified as being relevant to the device in question	
B9.2	Does the NB procedure allow for: (a) critical appraisal of the literature search and assessment of the validity of the manufacturer's conclusions (b) verification of the results of the literature search (c) reproduction of the literature search per protocol (d) check on the competence of the expert having evaluated the scientific literature/clinical data on behalf of the	

	manufacturer	
B9.3	Does the NB process include verification and documentation that the data presented is equivalent (based on the criteria outlined in MEDDEV 2.7/1) to the device under assessment?	
B9.4	Does the NB process address relating to assessment of scientific literature: Manufacturer's rationale for the clinical, technical and biological equivalence of similar devices?	
B9.5	Does the NB process relating to assessment of scientific literature data check the manufacturer has presented a literature search protocol addressing: (a) the sources of data that will be used and a justification for their choice (b) the extent of any searches of scientific literature databases (the database search strategy) (c) the selection/criteria to be applied to published literature and justification for their choice (d) strategies for addressing the potential for duplication of data across multiple publications	
B9.6	Does the NB process assess other sources of technical or other data that influence the clinical data identified by the manufacturer including the evaluation of non-clinical data (bench testing, <i>in vitro</i> and animal studies) as an input to the clinical data?	
B9.7	If no clinical data from the specific device is presented, does this process address that the clinical data presented for equivalent devices when taken together with the available pre-clinical data is sufficient to demonstrate compliance with the Essential Requirements covering safety and performance of the device under normal conditions of use?	

	Does the NB specifically document this?	
B9.8	Does the NB process address that any gaps in the demonstration of compliance with the Essential Requirements or in demonstrating equivalence have been identified and resolved by the manufacturer?	
B9.9	Does this process address that the claims made in the device labelling are substantiated by the clinical data for equivalent devices taken together with the pre-clinical data?	
B9.10	Does this process address the validity of the data with respect to the author, study design and state of the art technologies?	

B10	NB assessment of data from clinical experience	
B10.1	Does the NB procedure allow for assessment of clinical data from the following sources at the time of certification and re-certification:	
B10.1.1	Manufacturer-generated post market surveillance reports, registries or cohort studies (which may contain unpublished long term safety and performance data)?	
B10.1.2	Adverse events databases (held by either the manufacturer or Regulatory Authorities)?	
B10.1.3	Data for the device in question generated from individual patients under compassionate use (e.g. as per 93/42/EEC Article 11.13) prior to marketing of the device?	
B10.1.4	Details of clinically relevant field corrective actions (e.g. recalls, notifications, hazard alerts)?	
B10.2	Does the NB have a specific process and established criteria for analysis of performance history and complaint analysis?	
B10.3	For clinical experience data from similar devices: Does the NB process address the manufacturer's rationale for the clinical, technical and biological equivalence of similar devices?	

B11	NB assessment of data from clinical Investigation	
B11.1	Does the NB process address the evaluation of manufacturer's data generated by a clinical investigation?	
B11.2	Does the NB assess and document whether or not the identified acceptance criteria of the investigation(s) have been met?	
B11.3	Does the NB check the data relating to the investigation outlined in section 6.3 of the MEDDEV, the final report in line with EN ISO 14155-1/2 and according to local requirements?	
B11.4	<p>Where relevant does the NB request from the manufacturer:</p> <ul style="list-style-type: none"> <li>(a) the clinical investigation plan</li> <li>(b) clinical investigation plan amendments and the rationale for these changes</li> <li>(c) the relevant Ethics Committee(s)' documentation, opinion(s) and comments for each</li> <li>(d) the investigator's brochure</li> <li>(e) details of the investigation sites, including a copies of the approved informed consent form(s) and patient information documents</li> <li>(f) case report forms, monitoring and audit records</li> <li>(g) Regulatory Authority approvals and associated correspondence as required by applicable regulations</li> <li>(h) the signed and dated final report</li> <li>(i) Confirmation that the investigators have had opportunity to review and comment on the final report</li> <li>(j) Confirmation that the final report has been sent to the regulatory authorities involved if required</li> </ul>	

B11.5	For evaluation of data from clinical investigations: Does the reviewer:	
B11.5.1	Critically evaluate the data generated from the CI?	
B11.5.2	Assess the methodology of the CI (appropriateness of the study design, compliance with EN ISO 14155-1/2)?	
B11.5.3	Check the compliance of the CI with the Clinical Investigation Plan/Protocol as provided to the CA and Ethics Committee?	
B11.5.4	Check deviations from the Clinical Investigation Plan/Protocol with, when relevant, rationale for deviation, notification to the CA and Ethics Committee and agreements from the CA/Ethics Committee to the changes or early termination of the CI?	
B11.5.5	Check that all serious adverse events have been reported in line with the requirements of the relevant Directive or local regulatory requirements?	
B11.5.6	Address statistical analysis of the CI?	
B11.5.7	Check, where the CI was performed outside of the EU, has the manufacturer demonstrated that the use of the device and the patient population are representative to those for which the device will be used within the EU?	
B11.5.8	Check that the manufacturer has ensured that the principles of the Helsinki Declaration have been applied?	
B11.6	Does the NB sample data points (e.g. Case Report Forms) to ensure compliance with the Clinical Investigation Plan/Protocol ensuring traceability of the data?	



B11.7	Does the NB evaluate and document the adequacy of the clinical data submitted to determine if:	
B11.7.1	The identified acceptance criteria of the investigation(s) have been met?	
B11.7.2	The manufacturer's evaluation of the data has led to valid conclusions being drawn?	
B11.7.3	The data verifies the performance characteristics of the device under the normal conditions of use?	
B11.7.4	The data demonstrates compliance with the aims/objectives of the CI, and the Essential Requirements of the relevant Directive?	
B11.7.5	The manufacturer has defined a list of identified hazards to be addressed, provided an adequate estimation of associated risks for each identified hazard and a decision on the acceptability of the risks for each hazard? Have these hazards been addressed with the data?	
B11.7.6	The risk-benefit analysis of the device under the normal conditions of use (to take account of other 'state of the art' devices, technologies and procedures) has demonstrated that the risks are acceptable when balanced against benefits to the patient?	
B11.7.7	The claims made in the device labelling are substantiated by clinical data?	

<b>B12</b>	<b>Notified Body's Report (review of clinical data Annex II.4 and III)</b>	
B12.1	Does the NB report on their assessment of a clinical evaluation meet the content requirements outlined in NBOG BPG 2009-1 and detailed in section 10 of MEDDEV 2.7/1?	
B.12.2	<p>Does the NB report record</p> <ul style="list-style-type: none"> <li>(a) whether the clinical evaluation documentation was complete and adequate</li> <li>(b) whether the clinical evaluation was conducted in accordance with MEDDEV 2.7/1 and the relevant Directive</li> <li>(c) the NB's verification of each step of the clinical evaluation process, from scoping, choice of route(s), identification, appraisal, analysis and overall assessment of the clinical data, to concluding and reporting</li> <li>(d) the NB's assessment of the clinical investigation data and/or literature review assembled, relevant procedures and compliance to relevant standards</li> <li>(e) the NB verification that the device has met the claimed performance/intended use and side-effects and risks have been properly evaluated</li> <li>(f) the NB's assessment of the clinical safety, performance and benefit/risk ratio</li> <li>(g) the NB's assessment of the conclusions drawn by the manufacturer from the clinical data presented</li> <li>(h) the NB's assessment of the validity of the clinical evaluation and its steps</li> <li>(i) the NB's conclusions on the clinical evaluation, documenting each step in the decision making process as per section 10.1.1 of MEDDEV 2.7/1</li> </ul>	

B12.3	Does the NB document the opinion of all experts involved and provide a rationale if the expert opinion is not or only partly observed?	
B12.4	Does the NB report document that the clinical evaluation data presented is sufficient to comply with to the relevant Essential Requirements?	
B12.5	Does the NB require that all clinical assessors sign and date the report?	

References	Directive 93/42/EC*, Directive 90/385/EEC*, *as amended
Sources	[1] <a href="#">NBOG BPG 2009-4</a> Guidance on Notified Body's Tasks of Technical Documentation Assessment on a Representative Basis [2] <a href="#">MEDDEV 2.7/1 Rev. 3</a> Evaluation of Clinical Data: A guide for manufacturers and notified bodies [3] <a href="#">MEDDEV 2.7/2</a> Evaluation of Clinical Data: A guide for manufacturers and notified bodies – Appendix 1 Clinical evaluation of coronary stents [4] EN ISO 14155-1 : 2003 Clinical investigation of medical devices for human subjects – Part 1: General requirements, EN ISO 14155-2 : 2003 Clinical investigation of medical devices for human subjects – Part 2: Clinical investigation plans [5] <a href="#">MEDDEV 2.12/2</a> Guidelines on post-market clinical follow up [6] <a href="#">MEDDEV 2.12-1 Rev. 6</a> Guidelines on a medical devices vigilance system [7] <a href="#">NBOG Designating Authorities Handbook</a>
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