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Clinical evaluation under EU MDR

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Contents

1. Introduction and background

There has been significant evolution in the European regulatory landscape over the past 10–15 years, particularly with respect to requirements for clinical evaluation. These changes have been driven in part by a series of medical device failures, which fuelled a perception, particularly amongst regulators and clinicians, that clinical evidence for medical devices was not receiving sufficient scrutiny in Europe.

One of the early markers of this shift came with the publication of Directive 2007/47/EC in September 2007, which amended the European Active Implantable Medical Devices Directive (90/385/EEC, EU AIMDD) and the European Medical Devices Directive (93/42/EEC, EU MDD). Although the scope of Directive 2007/47/EC was not limited to clinical evaluation, many of the amendments had a direct impact on clinical evaluation and postmarket data collection. Amongst these were:

- A new definition of 'clinical data' was added to Article 1 of both Directives, including a specification of acceptable sources of clinical evidence.
- The requirement for demonstration of conformity with the Essential Requirements (ERs) to include a clinical evaluation was moved from the 'design and construction' specific section of Annex 1/I to the 'general' section. The implication of this change was that clinical evaluation was an explicit requirement for all devices, regardless of design or intended purpose.
- Substantial amendments were made to Annex 7/X (clinical evaluation), including:
    - clinical investigation required by default for all Class III and implantable devices; any decision not to undertake a clinical investigation for these devices must be duly justified
    - clinical evaluation must be documented as part of the technical documentation
    - the clinical evaluation and its documentation must be actively updated with data obtained from postmarket surveillance
    - if postmarket clinical follow-up is not deemed necessary, this must be duly justified and documented.

Following the publication of Directive 2007/47/EC, there came a succession of new and revised guidance documents and legislation. The intent of many of these changes was to improve the quality of medical device clinical evaluations and the scrutiny to which they were subject. Table 1 is intended to be illustrative rather than exhaustive.

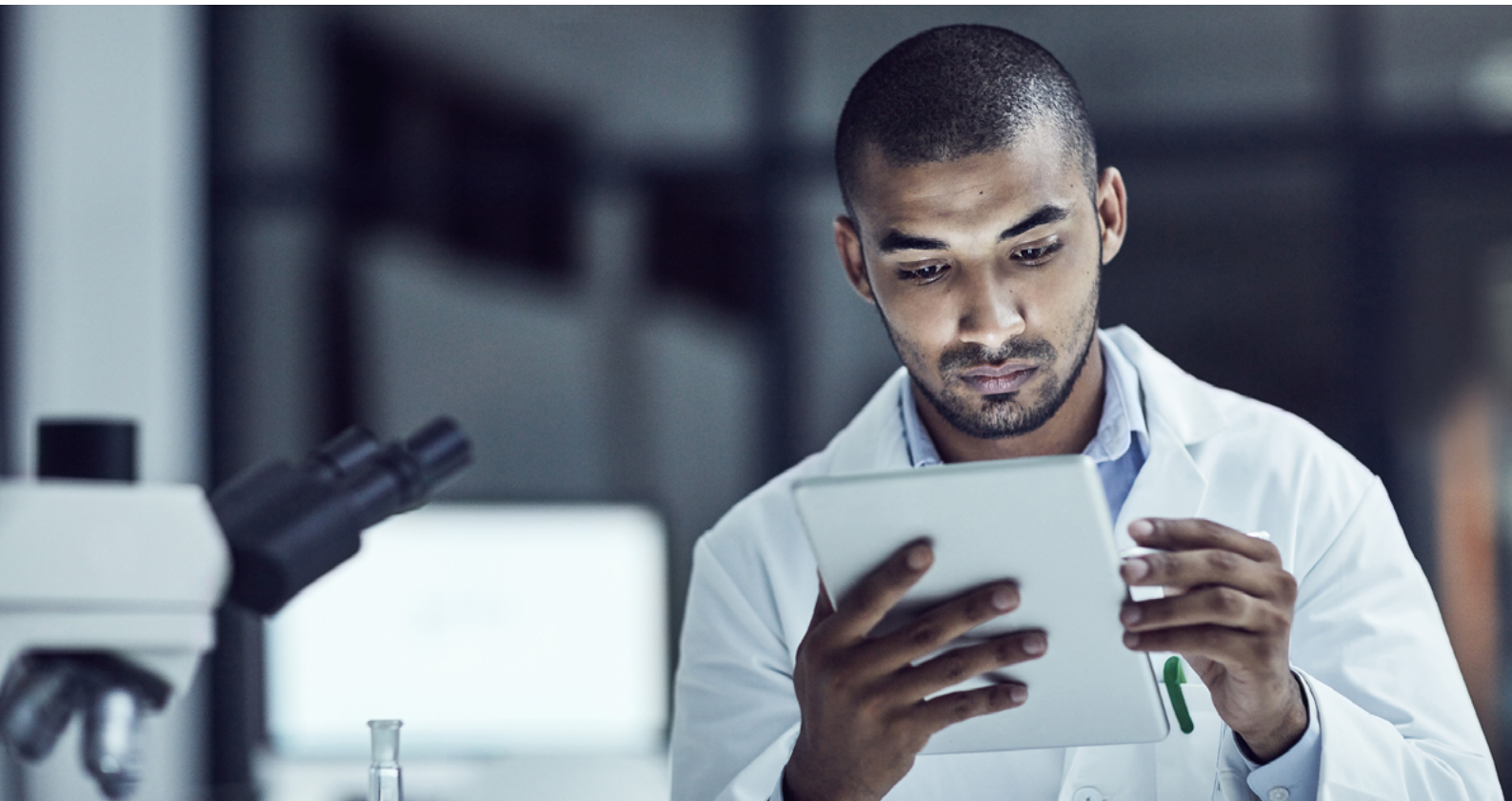


Table 1: Timeline of regulations and guidance impacting clinical evaluation assessments from 2009–present

Year	Document	Impact on clinical evaluation assessments
2009	MedDev 2.7/1 rev 3	Significantly greater content provided regarding the clinical evaluation process, data appraisal and analysis and validity of conclusions (increase from 19 to 46 pages)
2010	NBOG CL 2010-1	Publication of detailed checklist for competent authorities to audit notified body competence to undertake clinical evaluation assessments
2013	Implementing Regulation 920/2013	Begins to increase specificity of clinical experience required in notified body clinical evaluation conformity assessments
2014	NBOG BPG 2014-2	
2016	MedDev 2.7/1 rev 4	Further expansion of the guidance, to reinforce concepts around quality and completeness of clinical data and scientific validity of conclusions (increase from 46 to 65 pages)
2017	Regulation (EU) 2017/745	Clinical evaluation requirements largely aligned with MedDev 2.7/1 rev 4 become enshrined in EU law
	NBOG BPG 2017-2	Further increases specificity of clinical experience required to undertake a notified body clinical evaluation assessment
2020	MDCG 2020-5 MDCG 2020-6	Guidance reinforcing key clinical evaluation requirements from MedDev 2.7/1 rev 4 and Article 61 and Annex XIV Part A of the EU MDR
	MDCG 2020-13	Clinical evaluation assessment report template, specifying recommended minimum content for a notified body clinical evaluation assessment

Cumulatively these changes have shaped and reinforced the current practices, particularly with respect to parameters which affect the validity of the process and conclusions drawn:

- scope and clinical evaluation planning
- data collection methods
- data appraisal and analysis
- data mapping, benefit-risk evaluation and conclusions on 'sufficient clinical evidence'

Much information is available regarding systematic review methodology from which these requirements have been drawn; this white paper will therefore focus on the purpose of the clinical evaluation, some of the embedded requirements that may not be immediately obvious to all manufacturers, and in particular the importance of clinical evaluation planning and scope.

2. Purpose of a clinical evaluation

Article 61(1) of the EU MDR indicates that manufacturers 'shall plan, conduct and document a clinical evaluation' to enable:

> *Confirmation of conformity with relevant general safety and performance requirements … under the normal conditions of the intended use of the device, and the evaluation of the undesirable side-effects and of the acceptability of the benefit-risk ratio … shall be based on clinical data providing sufficient clinical evidence*

This fits well with the definition of 'clinical data' in Article 2(48), which implies that the purpose of the clinical evaluation is 'to verify the safety and performance, including clinical benefits, of the device when used as intended by the manufacturer'.

However, this is not the complete picture. Synthesizing the requirements from Article 61 and Annex XIV of the EU MDR with the additional clarifications provided by guidance such as MDCG 2020-5 and 2020-6, the clinical evaluation must also:

- Clearly identify the intended purpose and associated clinical benefits of the device(s) as well as the conditions of use and specific contraindications, in a way that can be justifiably supported by the available clinical evidence
- Establish outcomes achievable with other state of the art (SOTA) therapies for the same patient populations and treatment indications, to determine benchmarks for safety, performance and benefit-risk of the subject device
- Justify the sources of data used, including use of equivalence and non-clinical evidence, if applicable
- Draw conclusions not only regarding safety, performance and benefit-risk, but justify the completeness of the evidence to support:
    - all indications (including those implied by broad intended purpose statements)
    - all potential patient populations, with particular reference to high risk or vulnerable populations
    - all device variants and combinations
    - usage with accessories and other devices, where applicable
    - device lifetime in use
    - risk identification/confirmation of risks identified through the manufacturer's risk management processes
    - acceptability of residual risks

Stated more succinctly, the purpose of the clinical evaluation is to demonstrate, with objective and scientifically valid evidence, that the device does what it is supposed to do, achieves its intended clinical benefits (whether direct or indirect) and that the benefit-risk conclusion is acceptable in comparison to other available therapeutic or diagnostic options.

[1] McKinsey & Company: The construction productivity imperative, June 2015»

3. Overview of the clinical evaluation process

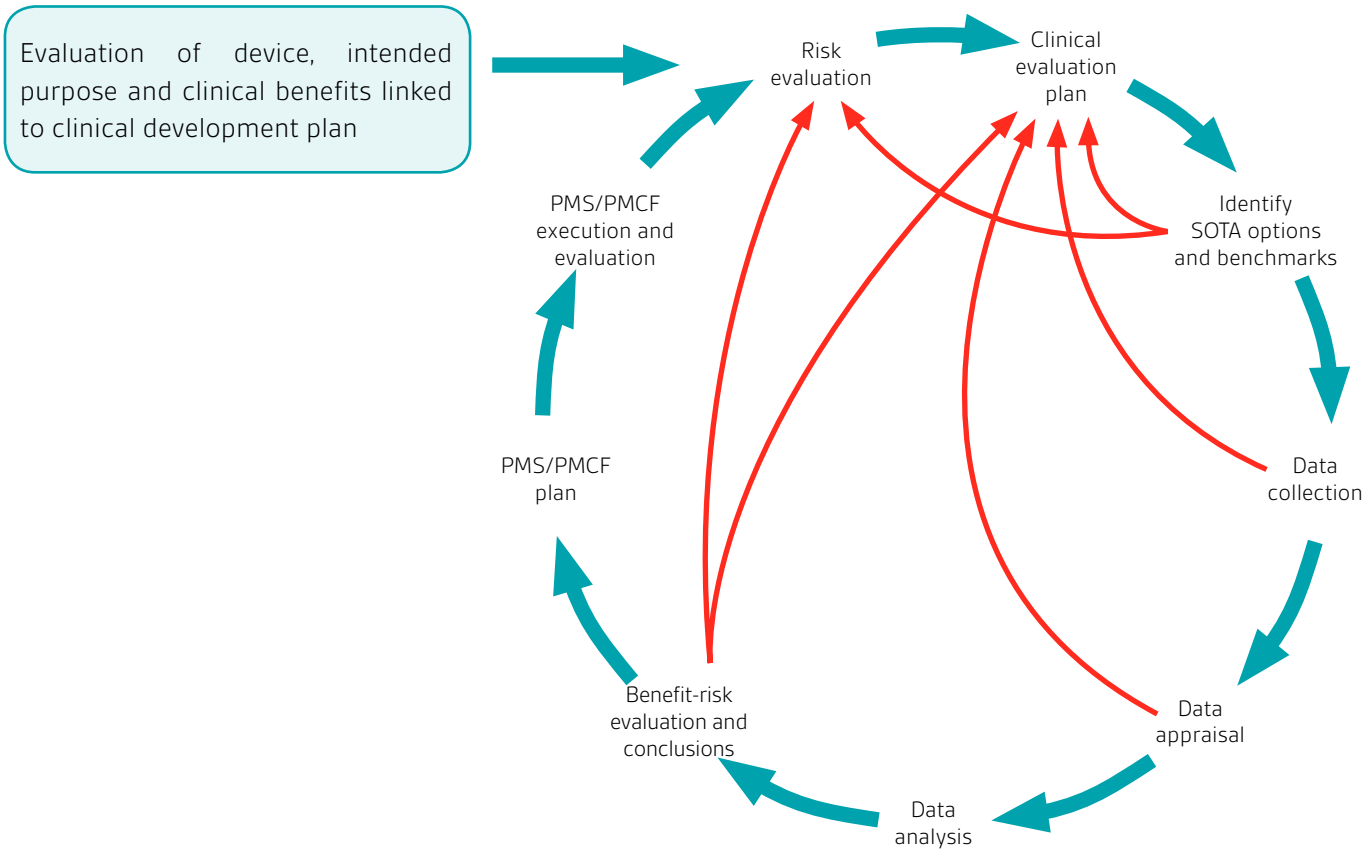
Annex XIV of the EU MDR defines the requirements for the clinical evaluation process. These are largely consistent with the process as described under EU AIMDD and EU MDD and expanded in the MedDev 2.7/1 guidance: planning, data collection, data appraisal, data generation (if indicated), data analysis and conclusions, continued data collection in the postmarket phase to maintain and update the clinical evaluation.

Although this sequence is frequently depicted as a neat, sequential, step-by-step process, in practice interdependencies may create feedback loops within the cycle. Examples of such interdependencies include:

- outputs from the SOTA evaluation may indicate revisions to the risk evaluation or clinical evaluation plan are required prior to the collection of further postmarket data
- there may be no relevant data identified at the data collection stage, necessitating a re-evaluation of the clinical evaluation or clinical development plan
- following data appraisal, it may become apparent that there is not sufficient literature to feed into data analysis, which may then prompt a revision of the clinical evaluation plan
- conclusions from the clinical evaluation may indicate a revision to the clinical evaluation plan, such as additional pre-market studies or a change to the indications for use, or a revision to the risk analysis and related risk management documentation

Potential interdependencies are illustrated in Figure 1:

Figure 1: Interdependencies and potential feedback loops within the clinical evaluation process



4. Clinical evaluation planning

Planning is essential to an effective clinical evaluation process. To demonstrate that a device achieves its intended performances, clinical benefits and safety specifications, it is necessary first to identify what these parameters are. The manufacturer must then explain how those parameters can be measured or demonstrated (i.e. what the associated endpoints are), and what an acceptable outcome looks like (i.e. benchmarks or performance measures). To do this, it is necessary to start with a clear and sufficiently detailed description of the device's intended purpose, and a specification of the standard of care for that intended purpose (otherwise referred to as the 'state of the art').

4.1. Intended purpose, indications, contraindications

The definition of the intended purpose and indications for use of the device is a critical first step which shapes all subsequent aspects of the evaluation: it defines the objectives of the evaluation, the scope of associated literature searches, the scope of the risk evaluation, criteria for selection of SOTA devices and therapies and ultimately the evaluation of the sufficiency of the clinical evidence.

4.1.1. Historical context: intended purpose and indications under the Directives

The EU AIMDD and EU MDD both defined *'intended purpose'* as *'the use for which the device is intended according to the data supplied by the manufacturer on the labelling, in the instructions and/or in promotional material'*. Frequent reference to 'intended purpose' was made in both Directives, linking it inextricably to demonstration of conformity to the ERs and the clinical evaluation. However, no mention was made of medical indications, other than a single reference to 'contra-indications' in each Directive. This led some manufacturers to interpret 'intended purpose' to mean 'the action performed by the device' or 'how the device is used', with no reference to other parameters such at the intended patient population, treatment indications, end stage and severity of disease, etc. For example, the intended purpose of a lumbar fusion cage could theoretically be defined as 'to provide stabilization and to allow or enable fusion between two adjacent lumbar vertebral bodies when used with autogenous and/or allogeneic bone graft material'. However, without a definition of the indications for lumbar fusion, it is extremely difficult to demonstrate a satisfactory benefit-risk conclusion. The risks associated with spinal surgery, for example, may be acceptable when weighed against the benefits for a patient with intractable pain and disability due to grade IV spondylolisthesis, whereas a patient with mild to moderate degenerative disc disease may respond well to less invasive therapies. The intended purpose statement must be unambiguous and include only those indications for which a positive benefit-risk conclusion can be demonstrated.

4.1.2. Intended purpose and indications under the EU MDR

Although Article 2(12) of the EU MDR provides the same definition of 'intended purpose' as the former Directives, Annex I Section 23.4 confirms that the intended purpose includes indications, where these exist:

> *The instructions for use shall contain all of the following particulars:*
> ...
> *(b) the device's intended purpose with a clear specification of indications, contra-indications, the patient target group or groups, and of the intended users, as appropriate*

It is important to note that not all devices have indications, as clarified by the definition of 'indication' in MDCG 2020-6:

> *'indication', 'indication for use': refers to the clinical condition that is to be diagnosed, prevented, monitored, treated, alleviated, compensated for, replaced, modified or controlled by the medical device. It should be distinguished from 'intended purpose/intended use', which describes the effect of a device. All devices have an intended purpose/intended use, but not all devices have an indication (e.g. medical devices with an intended purpose of disinfection or sterilisation of devices).*

However, where a device does have indications, confirmation of conformity with the relevant General Safety and Performance Requirements (GSPRs) of Annex I must include clinical data relating to these indications. Annex XIV Section 1a specifies that the clinical evaluation plan must include *'a clear specification of intended target groups with clear indications and contra-indications'* and

> *an indicative list and specification of parameters to be used to determine, based on the state of the art in medicine, the acceptability of the benefit-risk ratio for the various indications and for the intended purpose or purposes of the device*

It is therefore clear that broad intended purpose statements will not be satisfactory for most devices under the EU MDR.

Manufacturers may be unsure of the level of specificity required for the definition of intended purpose, indications and contraindications. For example, is it necessary to specify all anatomic locations in which a suture may be used? To what extent should a transcatheter aortic valve replacement specify the grade and severity of aortic stenosis for which it is indicated? Should a CT scanner specify every disease condition for which it might be used as an aid to diagnosis?

A useful guiding principle is to consider not just the intended purpose of the device, design principles and mechanism of action, but the standard of care and risks associated with any given potential indication or application. The greater the unknown unknowns and potential risks, the greater the need for specificity in the intended purpose statement.

4.2 Intended/expected clinical benefit

4.2.1. Regulatory context

An important consideration closely associated with intended purpose and indications is the intended clinical benefit. EU MDR Article 2(53) defines clinical benefit as

> *the positive impact of a device on the health of an individual, expressed in terms of a meaningful, measurable, patient-relevant clinical outcome(s), including outcome(s) related to diagnosis, or a positive impact on patient management or public health.*

The definition of 'clinical evaluation' in Article 2(44) confirms that it is meant to include the verification of clinical benefit, not just safety and performance. In other words, it is not sufficient to demonstrate that a device can achieve its intended purpose safely, the manufacturer must also demonstrate that there is a meaningful, quantifiable benefit to using it. This is reinforced in Annex XIV, which requires the clinical evaluation plan to include *'a detailed description of intended clinical benefits to patients with relevant and specified clinical outcome parameters'*, and the clinical evaluation to *'analyse all relevant clinical data in order to reach conclusions about the safety and clinical performance of the device including its clinical benefits'.*

4.2.2. Direct vs indirect clinical benefits

Sometimes, the clinical benefit associated with a device is indirect: in other words, the device itself does not directly achieve the positive impact on the patients, but it enables a procedure to be undertaken, a therapy to be delivered or another device to achieve its intended purpose. To give a few examples:

- an IV line may facilitate delivery of chemotherapy drugs, but does not directly treat cancer
- a cutting guide for a knee joint replacement allows accurate bone cuts which may improve the clinical effectiveness of the implant, but it does not directly reduce pain or increase range of motion
- a guide catheter may allow a stent to be delivered but does not directly treat the symptoms of coronary artery disease

It can be challenging to define the clinical benefit for such devices. Considering each of the previous three examples:

- For an IV line, the clinical benefit may simply be that it allows administration of intravenous fluid, but this does not translate easily to a clinical outcome measure, as required by Annex XIV section 1(a) bullet four. In cases like this, it would make sense to interpret 'relevant clinical outcome measure' as the evidence that would be required to demonstrate the device is safe and performs as intended. That would most likely be a combination of design validation, compliance to standards and postmarket surveillance data.
- On the other hand, although a knee implant cutting guide does not directly reduce pain or increase range of motion in the intended patient, it can have a significant impact on short-, medium- and long-term outcomes of the implants. For this kind of device, the clinical benefit may be 'enables accurate placement of the implant'; demonstration of satisfactory safety, performance and clinical benefit of the implant could therefore be used by inference to demonstrate satisfactory safety, performance and clinical benefit of the instruments.
- The guide catheter falls in between the previous two examples. Guide catheters may be used in a variety of different procedures, and therefore cataloguing clinical outcomes for each of these procedures would not generally be considered feasible. However, there may be specific claims made for a given device, such as 'reduces vessel trauma'. These claims would be considered clinical benefits which should be linked to specific and measurable clinical outcome measures.

4.2.3. Broad or generic clinical benefits

Some devices are used in so many different kinds of procedures that it would not be practical or beneficial to define the clinical benefits associated with them. For example, a scalpel may allow resection of a malignant tumour, which may be associated with many direct clinical benefits – but there has not been a call from the Commission for manufacturers to list out every procedure in which a scalpel could be used, or to define the clinical benefits of these procedures. Similarly, CT scanners may be used in a wide variety of different imaging applications, and sutures in a wide variety of soft tissue approximations. In general, for these kinds of devices, the benefit is that they perform their intended function (with the implication being that there is a clinical benefit to doing so). As for some of the devices with indirect clinical benefits, it makes sense to interpret 'relevant clinical outcome measure' to mean the evidence that would be required to demonstrate the device is safe and performs as intended, requiring a combination of design validation, compliance to standards and postmarket surveillance data. Caution should be exercised with respect to device or intervention specific risks however. If there are specific intended purposes which are considered higher risk, or which require specific design features which are not generic to the device type, then these might either need to be explicitly contraindicated or to have associated with clinical evidence (with relevant clinical outcome measures) to demonstrate that the devices are suitable for these specific indications.

4.3. Clinical claims

'Claim' is not directly defined in the EU MDR, but a contextual definition can be inferred from how the term is used. For the most part, the word 'claim' is linked to intended purpose, safety, performance and clinical benefit (i.e. clinical claims). For example:

- Article 2(52) links the definition of 'clinical performance' to a device's ability to *'achieve its intended purpose as claimed by the manufacturer'*
- Article 7 with respect to claims prohibits manufacturers from misleading users or patients *'with regard to the device's intended purpose, safety and performance'*
- Annex XV section 2.1 requires clinical investigations to be performed in such a way as to *'confirm or refute the manufacturer's claims regarding the safety, performance and aspects relating to benefit-risk of devices'.*

That is, a clinical claim is not only what the device is purported to do but also any associated information the manufacturer provides with respect to how well or how safely it can do it. The term is not restricted to promotional claims or claims of superiority, but may include these, as implied by the definition of 'intended purpose' in Article 2(12):

> *the use for which a device is intended according to the data supplied by the manufacturer on the label, in the instructions for use or in promotional or sales materials or statements and as specified by the manufacturer in the clinical evaluation.*

It is important to ensure clinical claims are addressed by the clinical evaluation. Implied clinical claims without sufficient clinical evidence should be avoided and may be challenged. For example, if the intended purpose does not exclude paediatric populations, then clinical evidence would be expected to demonstrate that the device is suitable for use in this population. Certain design features may imply specific performances and clinical benefits, even if these are not explicitly stated by the manufacturer. For example:

- an antimicrobial coating on a vascular access port implies the device would reduce the risk of infection relative to an uncoated port, even if the manufacturer does not explicitly claim this
- the design specification of a rotating platform in a knee joint replacement implies improved kinematics compared to a fixed platform, and thus clinical benefits associated with that improved function
- a low-profile catheter could imply access to smaller diameter vessels, or reductions in vessel damage, which would have a direct impact on the intended purpose and clinical benefits

Best practice would be to ensure that the intended purpose is complete and accurate, and does not include any implicit claims. It is also important to explain the intent of specific design features, particularly where a product family includes several variants. This should provide a clear correlation between the device, its intended purpose, safety requirements, clinical benefits and the sources of evidence that will be needed to demonstrate that these are achieved.

4.4. Duration of use

A final potential pitfall to consider is the duration of use. Although it might be assumed that clinical follow-up should cover the device lifetime in use, there are many exceptions, including cases where follow up beyond the device lifetime is necessary. Table 2 provides a few examples.

Table 2: Considerations with respect to length of follow-up in relation to device lifetime and duration of expected clinical benefits and risks

Device	Duration of use	Considerations affecting length of follow-up
Spinal fusion cage	Lifetime of the patient	Bone remodelling is typically complete within 18–24 months of surgery, with many of the clinical benefits achieved within 3–6 months. 18–24 month data (with appropriate interim time follow-up intervals) could therefore be sufficient for initial CE marking, if the clinical consensus is that outcomes at this time point are reflective of long-term benefit-risk. However, adverse events may arise many years after fusion (and hence, device performance) is complete which may impact the benefit-risk conclusion. It would, therefore, normally be expected that postmarket surveillance would follow up safety outcomes over a much longer period.
Radiofrequency (RF) ablation for atrial fibrillation	Transient	Although device lifetime in use is the length of the procedure, postoperative procedural success would not be sufficient to demonstrate the safety and clinical benefit of the therapeutic device. There is currently no consensus statement regarding appropriate follow-up for these devices. Therefore, the length of follow-up should be justified based on how long the treatment effective is expected to last and what would be required to demonstrate a positive benefit-risk conclusion in comparison to other SOTA treatment options.
Advanced wound dressing for diabetic foot ulcers	7 days	While an individual dressing may be used for a maximum of seven days, it will be replaced with fresh dressing and the cumulative duration of use would extend over several weeks. As with the RF ablation example, the length of follow-up should be justified based on the wound healing cascade and what would be required to demonstrate a positive benefit-risk conclusion in comparison to other SOTA treatment options.
Hip replacement	Lifetime of the patient	Ideally the duration of use of this device is the remaining lifetime of the patient; ten years' follow-up is commonly used to demonstrate long term outcomes. This has been based in part on guidance from organizations such as NICE (National Institute for Health and Care Excellence), and outcomes reported from joint replacement registries such as the Swedish Hip Arthroplasty Registry and UK National Joint Registry. For new joint replacements, a shorter duration is often accepted (again, based on a justification of how well long-term outcomes can be predicted from the shorter length of follow up).

5. Establishing the SOTA and benchmarks for safety and performance

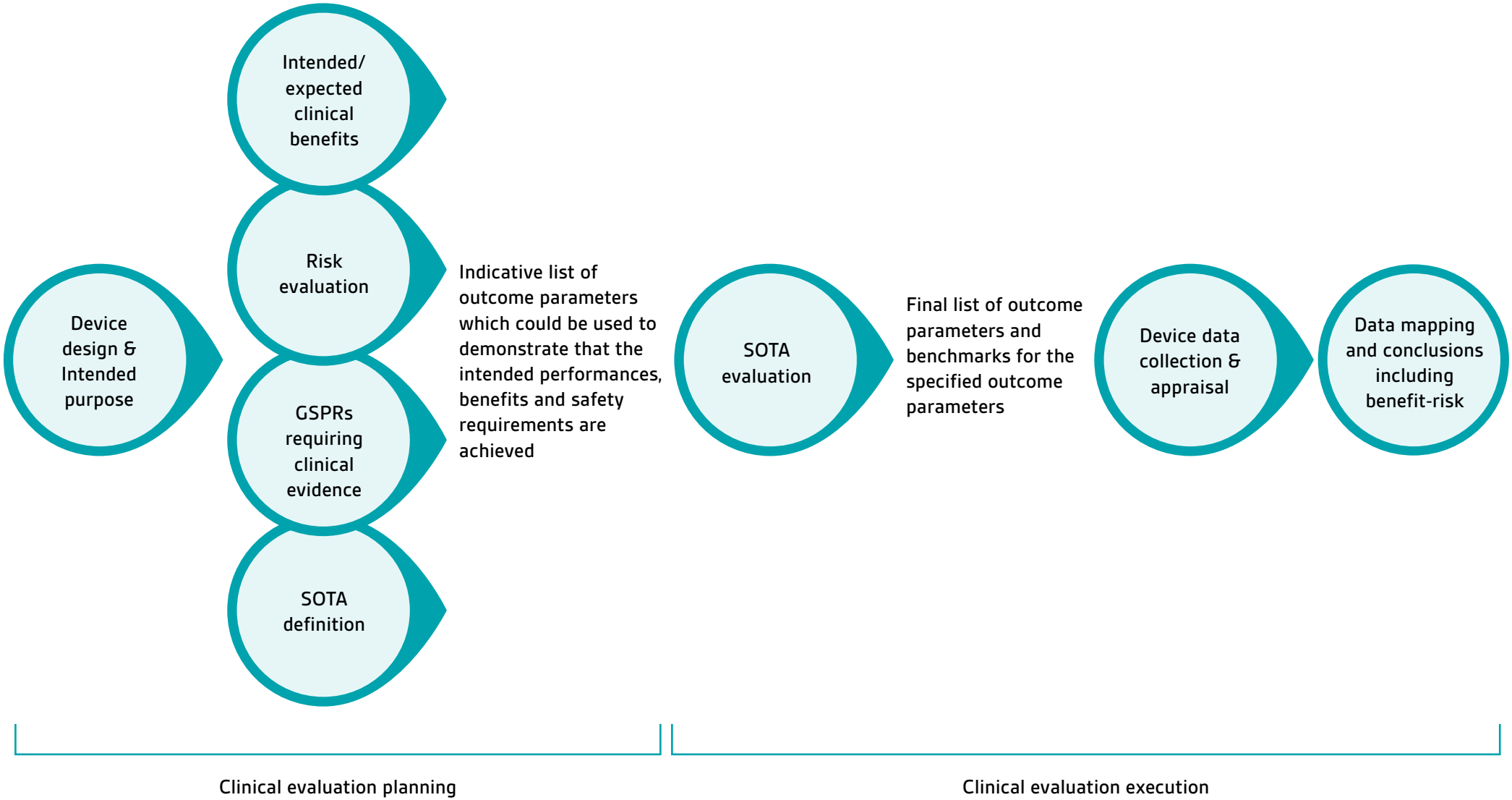
5.1. Purpose of the SOTA evaluation

The SOTA must be considered in the clinical evaluation planning and its evaluation completed during CER execution. As noted earlier, EU MDR Annex XIV section 1a requires, as part of clinical evaluation planning,

> *an indicative list and specification of parameters to be used to determine, based on the state of the art in medicine, the acceptability of the benefit-risk ratio for the various indications and for the intended purpose or purposes of the device.*

Special attention should be given to the word 'indicative'. The parameters cannot be fully defined until the SOTA evaluation has been completed. Therefore, during the initial clinical evaluation planning, several different outcome parameters may be proposed to demonstrate that a given safety, performance or clinical benefit has been achieved. Review of the SOTA enables this indicative list to be refined, and benchmarks to be established. This is the primary purpose of the SOTA evaluation: to define what 'acceptable' looks like for a given patient population. Evidence relevant to the safety, performance and benefit-risk determination for the subject device can then be mapped against these outcome parameters and benchmarks to demonstrate that they have been satisfactorily achieved, as illustrated in the process flow in Figure 2.

Figure 2: Process flow from design specification to intended performances and benefits, benchmarks, data evaluation and conclusions



'State of the art' as applied to medical device clinical evaluations should not be confused with the dictionary definition of state of the art. The Oxford English dictionary defines 'state of the art' as 'using the most modern or advanced techniques or methods; as good as it can be at the present time', whereas IMDRF/GRRP WG/N47 and MDCG 2020-6 provides the following definition:

> *Developed stage of current technical capability and/or accepted clinical practice in regard to products, processes and patient management, based on the relevant consolidated findings of science, technology and experience.*
>
> *Note: The state-of-the-art embodies what is currently and generally accepted as good practice in technology and medicine. The state-of-the-art does not necessarily imply the most technologically advanced solution. The state-of-the-art described here is sometimes referred to as the 'generally acknowledged state-of-the-art'.*

'State of the art', when applied to medical device clinical evaluations, can therefore be considered to be synonymous with 'standard of care'.

5.2. Devices with direct clinical benefits

For devices with a direct clinical benefit and specific treatment indications, the objective of the clinical evaluation is to demonstrate that the benefit-risk profile of device under evaluation is consistent with other SOTA treatment options. The identification of the SOTA should therefore be relevant to the specific patient populations and treatment indications associated with the device. For example, an implantable neuromodulator would only be used in cases of severe persistent neuropathic pain which has not responded to more conservative treatment options, so comparison to outcomes achievable with nonsteroidal anti-inflammatory drugs (NSAIDs) or physical therapy will not be meaningful. On the other hand, for a transcutaneous electrical nerve stimulation (TENS) machine indicated for treatment of 'low back pain, myofascial and arthritic pain, sympathetically mediated pain, bladder incontinence, neurogenic pain, visceral pain and postsurgical pain' of unspecified severity, a much wider range of therapeutic options should be included in the review of the SOTA.

It may sometimes also be possible to reference clinical or other best practice guidelines to determine benchmarks for clinical performance. For example, the NICE technology appraisal guidance on total hip replacement recommends a revision rate of 5 per cent or less at 10 years as the benchmark for survivorship of primary hip replacement prostheses. If such guidelines can be demonstrated to be appropriate within the European clinical and regulatory context, these may be used to establish benchmarks for the outcome parameters they reference.

5.3. Devices with indirect, broad or generic clinical benefits

If the purpose of the SOTA is to establish benchmarks for the *'relevant and specified clinical outcome parameters'* required by Annex XIV Section 1(a), how can this be achieved for devices with indirect, broad or generic clinical benefits? As described earlier, for such devices, the interpretation of 'clinical outcome parameter' may sometimes need to be a non-clinical parameter from which clinical safety or performance inferences can be made. This is supported by MDCG 2020-6, which states:

> *...while direct clinical benefits should be supported by clinical data, indirect clinical benefits may be demonstrable by other evidence such as:*
>
> - *pre-clinical and bench test data (e.g. compliance to product standards or common specifications)*
> - *real world data such as registries, information deriving from insurance database records, etc.*
> - *data from another device that is used with the subject device which does have direct clinical data (e.g. data from a stent used to justify safety and performance of a guidewire)*

SOTA benchmarks in these cases may be established through a variety of means, including:

- technical standards, pharmacopoeia or best practice guidelines which specify requirements for performance testing
- outputs of the risk management and design validation processes
- review of experience with similar devices, including literature and adverse events databases
- evaluation of complaint trending and signals

In all cases, the benchmarks established must be justified in light of the intended purpose, novelty and risks associated with the device.

6. The rest of the clinical evaluation process

Having defined a robust clinical evaluation plan, and specified relevant outcome parameters with appropriate benchmarks based on the SOTA, the rest of the clinical evaluation process is comparatively straightforward.

As indicated in the introduction to this white paper, so much has been written about systematic reviews, literature search methodology, data appraisal and analysis, that this paper will not attempt to expand on these topics, which are worthy of textbooks in their own right.

A few key points which may be useful to know for the creation of compliant clinical evaluation reports will however be touched on below.

6.1. Data collection

A variety of data sources may be used to demonstrate that a device meets requirements for safety, performance and clinical benefit. MDCG 2020-6 Appendix 3 provides a useful summary and hierarchy of evidence.

For almost all devices, some form of literature review will be required; for very low risk, standard of care devices, the purpose of the literature review may be simply to confirm that there is no relevant data published, and no new information with relation to the SOTA that would impact the risk evaluation or expectations for performance and clinical benefit.

However, it is worth pointing out that a few of the accepted literature sources as described in MedDev 2.7/1 rev 4 are still applicable under EU MDR, including:

- studies published via WHO International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov
- implant registry reports

and particularly with respect to SOTA evaluations:

- meta-analyses and reviews of health technology assessment (HTA) institutes and networks
- expert documents produced by professional medical associations
- harmonized standards and other standards applicable to the device in question and containing information on clinical performance and clinical safety

Under EU MDR, future sources of information may also include:

- studies published via the EUDAMED clinical investigations module
- common specifications applicable to the device in question and containing information on clinical performance and clinical safety
- opinions published by the Clinical Evaluation Consultation Procedure (CECP) expert panel.

6.2. Data appraisal and analysis

Section 1c of Annex XIV of EU MDR requires the manufacturers to: *'appraise all relevant clinical data by evaluating their suitability for establishing the safety and performance of the device'.*

In other words, the manufacturer needs to assess the quality of each data set, and justify its acceptability in light of the device's intended purpose, clinical benefits and associated risks.

Criteria that should be considered when appraising the data include:

- overall quality of the study design (where applicable)
- quality and completeness of the data presented
- potential sources of bias
- applicability of the data to the evidence requirements identified in the clinical evaluation plan
- applicability of the data to the device and how it is used

This appraisal can be used not only to determine whether a particular data set should or should not be included in the clinical evaluation but also to indicate a relative hierarchy of evidence. This is useful particularly when trying to determine the weight of evidence behind a given conclusion. In cases where there are conflicting studies or data sources, tools such as Forest plots may be used to resolve apparent discrepancies. It is important to ensure however that these activities are undertaken by individuals with appropriate expertise in study design and biostatistics, as the assumptions and methodology behind these activities are critical to ensure the validity of their conclusions.

6.3. Data mapping and conclusions, including benefit-risk evaluation

Once the data is appraised, it should be mapped against the relevant outcomes parameters and benchmarks identified through the cycle of SOTA evaluation and clinical evaluation planning. A critical aspect of this is to ensure that the data is appropriately stratified to enable conclusions to be drawn at the level of granularity implied by the device's intended purpose and specified through the clinical evaluation planning process. The extent of data stratification should be sufficient to enable conclusions on safety, performance and benefit-risk to be drawn for all device variants, combinations, treatment indications and patient populations, and to support any clinical claims specified by the manufacturer.

In some cases, a device may not meet the benchmark indicated by the SOTA evaluation for one or more outcome parameters. In these cases, the discrepancy may be addressed by:

- narrowing the scope or indications to those for which the benchmarks for clinical safety, performance and benefit parameters have been clearly met
- providing justifications for the applicability of other data sources to strengthen conclusions (e.g. potential applicability of data for one patient population to another population, additional equivalence routes, or cumulative clinical and non-clinical evidence as described in MDCG 2020-6 Appendix III)
- providing a quantification of benefit-risk (e.g. to demonstrate that the a risk reduction is so great as to outweigh a small reduction in benefit, or considerations relating to unmet needs and the risk to the patient of not having a given treatment option available)

It is normally expected that any benefit-risk conclusions that rely on justifications or data extrapolations will be supported by appropriate postmarket clinical follow-up (PMCF), to ensure data collection to confirm the conclusions drawn.

6.4. Frequent notified body findings

Frequent notified body findings on clinical evaluation reports include:

- Objectives of the clinical evaluation are too generic; specific and measurable objectives (SMOs) are required.
- Benchmarks for the SMOs have not been established in relation to the SOTA.
- Intended purpose statement is incomplete; clinical indications are unclear.
- Clinical evidence does not support the full breadth of the intended purpose.
- Clinical data has not been appropriately stratified against the intended patient populations, treatment indications, device variants and combinations and SMOs.
- Gaps in clinical evidence are not adequately justified.
- The benefit-risk conclusion is not justified in relation to the SOTA.
- The residual risks associated with the device have not been appropriately identified.
- The PMCF plan does not address the device residual risks.
- The justification for 'no specific PMCF' mechanism in accordance with Annex XIV section 6.2b is not acceptable.

Getting the proper scope and objectives at the outset of the clinical evaluation can go a long way to addressing these potential findings before they arise. Clear data mapping against the specified SMOs and benchmarks is also extremely helpful. Sometimes manufacturers are concerned that making a data gap too obvious by providing such a mapping will lead to unnecessary findings, but in practice, because the notified body reviewer must carefully document and justify their acceptance of the manufacturer's conclusions, the opposite is true. Transparency and accuracy, combined with appropriate justifications for the benefit-risk conclusions, will reduce the number of findings and delays to certification.

7. Acronyms

CECP: clinical evaluation consultation procedure
CER: clinical evaluation report
CT: computerised tomography
ER: essential requirement
EUDAMED: EUropean DAtabase on MEdical Devices
EU IVDR: European In Vitro Diagnostic Medical Device Directive
EU MDD: European Medical Devices Directive, 93/42/EEC
EU MDR: European Medical Devices Regulation 2017/745
GSPR: general safety and performance requirement
HTA: health technology assessment
ICTRP: International Clinical Trials Registry Platform
IV: intravascular
MDCG: Medical Device Coordination Group
NBOG: Notified Bodies Operations Group
NICE: National Institute for Health and Care Excellence
NSAIDs: nonsteroidal anti-inflammatory drugs
PMCF: post market clinical follow-up
SMO: specific and measurable objective
SOTA: state of the art
SSCP: summary of safety and clinical performance
TENS: transcutaneous electrical nerve stimulation
WHO: World Health Organization

8. References and related guidance

- Directive 2007/47/EC amending Council Directive 90/385/EEC on the approximation of the laws of the Member States relating to active implantable medical devices, Council Directive 93/42/EEC concerning medical devices and Directive 98/8/EC concerning the placing of biocidal products on the market
- Implementing Regulation 920/2013 on the designation and the supervision of notified bodies under Council Directive 90/385/EEC on active implantable medical devices and Council Directive 93/42/EEC on medical device
- MDCG 2019-9: Summary of safety and clinical performance. A guide for manufacturers and notified bodies
- MDCG 2020-5: Clinical Evaluation — Equivalence. A guide for manufacturers and notified bodies
- MDCG 2020-6: Regulation (EU) 2017/745: Clinical evidence needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC. A guide for manufacturers and notified bodies
- MDCG 2020-13: Clinical evaluation assessment report template
- NBOG BPG 2014-2: Guidance on the Information Required for Notified Body Medical Device Personnel Involved in Conformity Assessment Activities
- NBOG BPG 2017-2: Guidance on the Information Required for Conformity assessment bodies' Personnel Involved in Conformity Assessment Activities
- NBOG BPG CL 2010-1: Checklist for audit of Notified Body's review of Clinical Data/Clinical Evaluation

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