Medical Devices

SECTION EDITOR

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Editorial

Establishing a solid state of the art under the Medical Device Regulation (MDR) is complex and requires both experience and expertise. As medical writers across Europe have successfully put into practice their knowledge and interpretation of the MDR, getting to know the experiences of other medical writers continues to provide new perspectives and insights. In this article, the author shares her tips and tricks for establishing an MDR-compliant state of the art in the hope to provide useful tools to other medical writers. **Payal**

Mastering the art of the state of the art (under EU MDR 2017/745)

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Abstract

Establishing the state-of-the-art (SOTA) represents a crucial aspect of a clinical evaluation under the European Medical Device Regulation (EU MDR) 2017/745. In this article, I share my experience of working on SOTA documents over the last four years. It first briefly recapitulates the SOTA requirements of the EU MDR (that are in fact almost non-existent) followed by the different steps required to conduct and document the literature search. Also included are some tips and tricks on structuring the SOTA. Finally, advantages and limitations of different scientific literature databases are provided.

Introduction

The state-of-the-art (SOTA) literature review represents a crucial aspect of a clinical evaluation required not only to obtain CE marking but also to maintain CE marking in accordance with the European Medical Device Regulation (EU MDR) 2017/745. According to the Oxford English Dictionary, SOTA can be both a noun and an adjective that means:

> "Belonging or relating to the latest or the most sophisticated stage of technical development, having or using the latest techniques and equipment".

Despite this simple definition, establishing an MDR-compliant SOTA is complex and requires a strict methodology including different stages (data identification, appraisal, analysis). Not to forget, this demands both time and experience.

I started to work as a freelance medical writer almost 4 years ago, after 8 years of working in academia. As a PhD student and/or postdoc, we routinely gather, analyse, and report scientific data on specific topics from the literature. And this is technically what is required to establish a SOTA. However, it took me a lot of practice (and a lot of phone calls with other medical writers specialised in the field) to master all the aspects of the methodology.

> The SOTA needs to cover two main topics: (1) the clinical background of the medical conditions targeted by the device under evaluation (DUE), and (2) the description of historical/alternative treatments and clinical evidence related to benchmark devices.

EU MDR requirements regarding the SOTA

In the EU MDR,[1] the term "state of the art" is mentioned several times, but no concrete description of how to establish a SOTA is provided. Instead, it only suggests that establishing the SOTA is to present the context of the medical condition that your device is targeting.

To gather more information on this (and on other clinical topics), the European Commission published guidelines called MEDDEV. Among them, there is the MEDDEV 2.7/1 revision 4 called "CLINICAL EVALUATION: A GUIDE FOR MANUFACTURERS AND NOTIFIED BODIES UNDER DIRECTIVES 93/42/EEC and 90/385/EEC". According to this guideline,

> "The current knowledge/state of the art therefore needs to be identified and defined, possibly also relevant benchmark devices and medical alternatives available to the target population."[2]

Therefore, the SOTA needs to cover two main topics: (1) the clinical background of the medical conditions targeted by the device under evaluation (DUE), and (2) the description of historical and/or alternative treatments and clinical evidence related to benchmark devices (Figure 1). To cover these topics, a documented literature review should be performed with pertinent literature selected that is then analysed, evaluated, and reported.

Apart from the SOTA, a third literature review is also required by EU MDR 2017/745 the purpose of which is to establish safety and performance profiles of the DUE. In other words, the main objective of the clinical evaluation is to evaluate the level of clinical evidence available for the DUE in the context of the SOTA.

The MEDDEV 2.7/1 revision 4[2] recommends the following three steps to conduct a literature review:

- Stage 1 – Identification of pertinent data
- Stage 2 – Appraisal of pertinent data
- Stage 3 – Analysis of pertinent data

It also recommends providing:

> "Brief summary and justification of the literature search strategy applied for retrieval of information on current knowledge/the state of

the art, including sources used, search questions, search terms, selection criteria applied to the output of the search, quality control measures, results, number and type of literature found to be pertinent. Appraisal criteria used."

The international medical device regulators forum (IMDRF) is a voluntary group of medical device regulators from around the world, independent of the MDR, who also published a technical document regarding clinical evaluation in 2019 in which additional information on SOTA literature review can be found.[3]

Literature search strategy

Aim

Clinical background. The clinical background section aims to describe the natural course and consequences of the medical conditions concerned.[2] It is advisable to document the different clinical forms, stages, and severities of the conditions. Additionally, the frequency of the medical condition in the general population as well as in different subpopulations (age, gender, ethnicity, genetic predispositions, etc.) should also be described.

Alternative treatments and benchmarks devices. According to the MEDDEV 2.7/1 revision 4, this literature review should cover the following topics:[2]

- "Description of available therapeutic/management/diagnostic options, historical context and developments, summary of advantages and disadvantages of the different options, benefit/risk profiles and limitations in relation to the different clinical forms, stages, and severities of the medical conditions and in relation to different target populations.
- Description of the benefits and risks (nature, extent, probability, duration, frequency), acceptability of undesirable side-effects and other risks (including the nature, severity, probability and duration of acceptable harm).
- Hazards due to substances and technologies that could be relevant to the device under evaluation. The mechanisms of harm, clinical aspects of minimisation, and management of side effects and other risks.
- Types of users. Diverging opinions of professionals as to the use of the different medical options. Unmet medical needs".

Type of references to search

Clinical background. The literature related to the clinical background of a medical condition can be vast. Also, the prevalence of a disease can significantly change with time. Therefore, it is important to target the literature search to latest studies to only reflect the current knowledge regarding the medical condition. Public health agencies (such as World Health Organization, European and American Centers for disease control and prevention, etc.) as well as medical societies or associations specialised in a medical field or condition (e.g., European Hematology Association, European Glaucoma Society, American Cancer Society, etc.) publish and update evidence-based guidelines on a regular basis. These guidelines or standards typically contain the latest knowledge related to medical conditions and represent the highest quality source of references.

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However, these guidelines neither exist for all medical conditions nor cover all aspects of the medical conditions. In such cases, other references such as review articles can be considered.

Alternative treatments and benchmark devices. In addition to the clinical background, guidelines published by public agencies and medical agencies/associations can also cover most of the topics required for this section of the SOTA. Clinical evidence of benchmark devices can be found in clinical studies, meta-analyses or systematic reviews if they are well-established

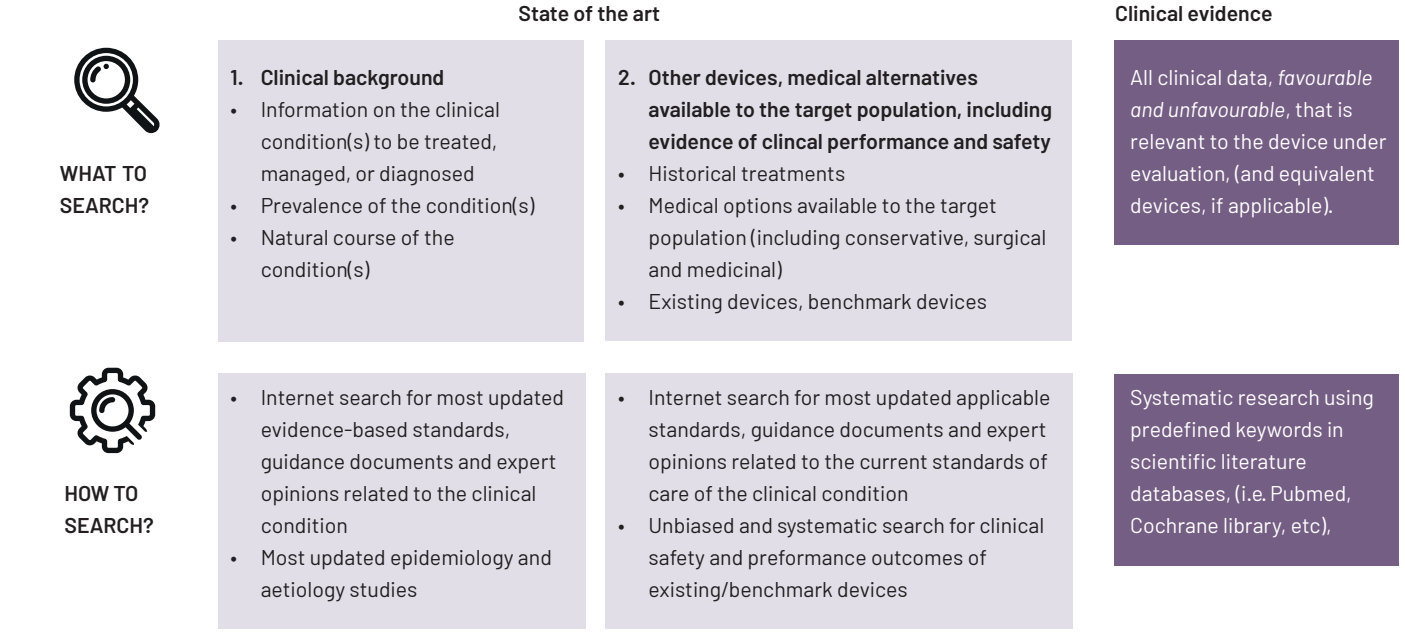

Figure 1. Literature search and review required for the clinical evaluation of medical devices under Regulation (EU) 2017/745

devices. The label, instructions for use and implant registries of benchmark devices (where available) should be also searched to establish their benefit/risk profiles.

Stage 1 – Identification of pertinent data

Guidelines and standards. Finding the latest evidence-based guidelines and/or standards is my very first step when I start to prepare a SOTA. Of course, the guidelines need to be up to date; I consider guidelines up to date when they have been published in the last 5 years. I make sure to use/cite only the latest version published by the agencies or societies/associations. To find them, I usually use search terms such as "diabetes AND (guidance OR guideline OR standard)". Alternatively, the websites of public agencies or medical societies/associations can be searched to find these guidelines. In some cases, the term "guideline", "guidance" or "standard" are used in the title of a document but are not officially written by medical entities. Therefore, as a quality control check, it is important to check the author's affiliation. To find pertinent review papers, the name of the condition can be used as a search term in scientific literature databases (e.g. PubMed). A selection criterion can also be added to only target "review papers". To find specific data on the prevalence of a medical condition or on the current standard of care, the search can be narrowed down by adding the term "prevalence" or "standard of care" in the search.

Review articles. If no guidelines exist regarding the clinical background or current alternative treatments, this can be found in review papers. To find them, I use straightforward search terms such as "[medical condition] AND "treatment" with a selection criteria for "review". However, it is important to make sure there is no bias in the review articles and this is why it is important to check author affiliations to detect potential conflicts of interest. It is crucial to not rely on a single review article since it may not cover all information. Instead, data from several review articles should be combined to describe the panel of existing alternative treatments as well as their benefit/risks profiles. To obtain more information about a specific alternative treatment, an additional literature search can be conducted using the name of the treatment. Clinicaltrial.gov also represents a useful tool to find any new clinical trials in a specific therapeutic area that use more recently developed devices.

Systematic literature review for benchmark devices. A systematic literature review should be conducted to gather all favourable and unfavourable clinical evidence related to the safety and performance of identified benchmark devices. The choice of search terms is key at this stage: they should be broad enough to capture all clinical evidence related to the benchmark device but not too generic resulting in unrelated hits. If a clinical study has been conducted and published on a medical device, the brand name of the device is most often mentioned in the abstract, but it is not always the case. For the search period, the date of commercialisation of the device can be used to make sure to gather all safety and performance outcomes reported in the literature. For the choice of the database, MEDLINE or Pubmed represents the main sources of literature. However, the MEDDEV 2.7/1 revision 4 guideline indicates that these databases may not cover all European journals. Therefore, other databases such as EMBASE/ Excerpta Medica or the Cochrane CENTRAL trials register should also be considered. A pre-screening should be conducted by reviewing all titles and abstracts of the results obtained after the search. At this stage, I exclude all results that do not refer to the benchmark device or that are not related to the safety or performance of the device. Then, the full document of the remaining results should be obtained for the appraisal phase. Finally, the label, instructions for use (IFU), or implant registries of the benchmark devices (where available) can be found directly on the website of the manufacturers or obtained by using internet searches.

> There is no "magic formula" to write a SOTA and since every medical device is different, the approach and methodology to establish the SOTA will vary.

Stage 2 – Appraisal of pertinent data

The methodology to appraise pertinent data described in the MEDDEV 2.7/1 revision 4 or in the IMRDF technical document mainly applies to clinical data of the DUEs, similar devices, and other devices. This system of appraisal is provided as guidance and can be adapted. As the clinical background is not used to assess the DUEs directly, it may not be extensively appraised. I include in the SOTA all guidelines published by public agencies and medical agencies/associations related to the medical condition since they represent the highest level of clinical evidence. For review articles and epidemiology studies, I try to detect any potential bias (e.g. subjective statements in favour of a treatment) and/or inadequate disclosure of information. It is also important to check the conflict of interests of the authors to ensure that an unbiased clinical background is presented.

Stage 3 – Analysis of pertinent data

Once sources of data have been identified and appraised, the last phase is to prepare a literature review of the SOTA. It is important to report all aspects of the clinical background described in all identified sources. I also try to add as much quantitative data as possible to provide an objective analysis. Moreover, the literature review of the available alternative and historic treatments should reflect all the aspects covered by the sources identified during the previous phases. It is essential to report a quantitative analysis of each clinical outcome reported for benchmark devices. Similar outcomes should be reported in the SOTA and in the section related to the clinical evidence of the DUE so that the safety and performance profiles of the latter can be assessed in the context of the clinical evidence of the benchmark devices. To report the clinical evidence related to benchmark devices, I typically prepare a table using the PICO classification criteria:

- Population(s)/disease(s) or condition(s)
- Intervention(s)
- Comparator group(s)/control(s)
- Outcome(s)/Endpoints(s)

In each column, I summarise only the main information (without overpopulating the table) and give a clear view of the clinical studies related to the benchmark device. It's important to detail all relevant outcomes/endpoints used in each study, and to provide the key results. Ideally, all results should be provided in the same units so they can be better compared between benchmark devices and most importantly with the DUEs. When a result with a different unit is provided, and when possible, I report the result as reported in the study and add a conversion to a more used unit. After the table, a conclusion containing the number and types of studies, as well as the key outcomes/endpoints should be presented. I also highlight in the conclusion the homogeneity among the studies, which helps draw scientifically sound conclusions.

Pros and cons of different databases for literature review

Choosing the right databases to conduct a literature review, including the ones required to establish the SOTA, can be tricky. In this section, I present the advantages and limitations of the

Table 1. Advantages and limitations of different scientific literature databases that can be used to conduct literature search under the EU MDR

Scientific literature database	Advantages	Limitations
Pubmed / MEDLINE	• Contains more than 37 million references • Multiple selection criteria to target the search • Provides options to export results as an Excel file (and other formats) • Search output compatible with reference managers such as EndNote • Free	• May not cover all European journals, especially the ones reporting user experience • Not all articles may have been indexed properly resulting in loss of evidence
Embase	• Contains over 29 million records from 8,500 journals (include MEDLINE database) • Multiple selection criteria to target the search	• Not free
Cochrane CENTRAL	• Contains only high-level-evidence articles including Cochrane systematic reviews, Cochrane protocols, clinical trials, clinical answers, and others • Free	• Limited to Cochrane publications
Google Scholar	• Covers more references than the other databases	• Search output cannot be properly documented • Not officially accepted by notified bodies as the primary database • Search output varies with every search • Not all references are peer-reviewed (trade/white papers, interviews, etc.)

four most commonly used databases in medical writing (Table 1).

In summary, no one database is better than the other, and no database should be used exclusively. Moreover, it is important to justify why the chosen database is the most appropriate choice for the given literature search.

Conclusion

There is no "magic formula" to write a SOTA and since every medical device is different, the approach and methodology to establish the SOTA will vary.

Nevertheless, some key points are common to every SOTA and include having an objective approach, adapting the literature search to the context (type of medical condition, quantity and type of data available, etc.), and justifying the methodology used (choice of database, quality control, inclusion/exclusion criteria, etc.). In-depth knowledge of the MEDDEV 2.7/1 revision 4 guideline is essential to understand all the aspects of the methodology needed to conduct and report a literature review under the EU MDR.

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Disclosures and conflicts of interest

The author declares no conflicts of interest.

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