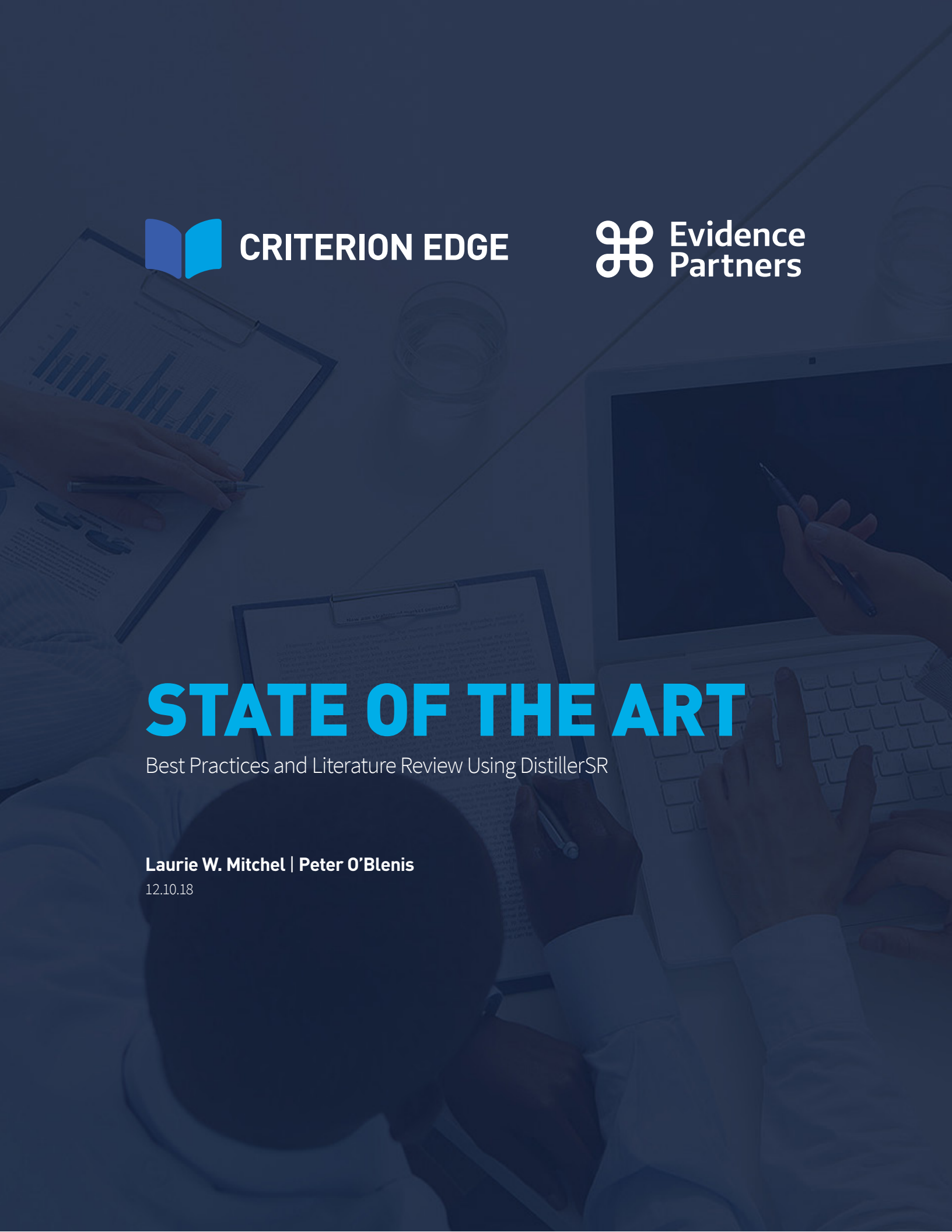

CRITERION EDGE

Evidence Partners

STATE OF THE ART

Best Practices and Literature Review Using DistillerSR

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12.10.18

The regulatory framework which governs market access to the European Union (EU) is undergoing far-reaching changes with the May 2017 publication of the EU Medical Device Regulation 2017/745 (MDR). This publication replaces the EU's Medical Device Directive (93/42/EEC) and the EU Directive on active implantable medical devices (90/385/EEC). The current 3-year grace period for meeting MDR requirements will expire when the MDR comes into force in May 2020. Key changes coming into effect with this regulation include reinforced rules on clinical and performance evaluation, clinical investigation and performance studies, technical documentation and labeling, quality assurance, risk management and postmarket expectations.

To comply with new European MDR and associated MEDDEV guidance document 2.7/1, which was released in revision 4 in 2016 ("MEDDEV 2.7.1 rev 4"), manufacturers are expected to demonstrate that they have conducted a thorough clinical evaluation of the device. The MDR defines this as systematic and planned process to continuously generate, collect, analyse and assess the clinical data pertaining to a device in order to verify the safety and performance, including clinical benefits, of the device when used as intended by the manufacturer.

As part of this process, manufacturers are required to demonstrate that they have conducted a thorough analysis of the current state of the art, to comply with the number one general requirement which states that devices "shall achieve performance [. . .] taking into account the generally acknowledged state of the art" (MDR ANNEX I, Ch I, 1).

Preceding the publication of the MDR, MEDDEV 2.7/1 rev 4 has provided detailed guidance to what is referred to as "current knowledge/state of the art". State of the art, or state-of-the-art, is commonly used to describe the best, cutting edge, or, per Merriam Webster, "the highest level of development (of a device, procedure, process, technique, or science) reached at any particular time, usually as a result of modern methods".

But what does it mean for the clinical evaluation process?

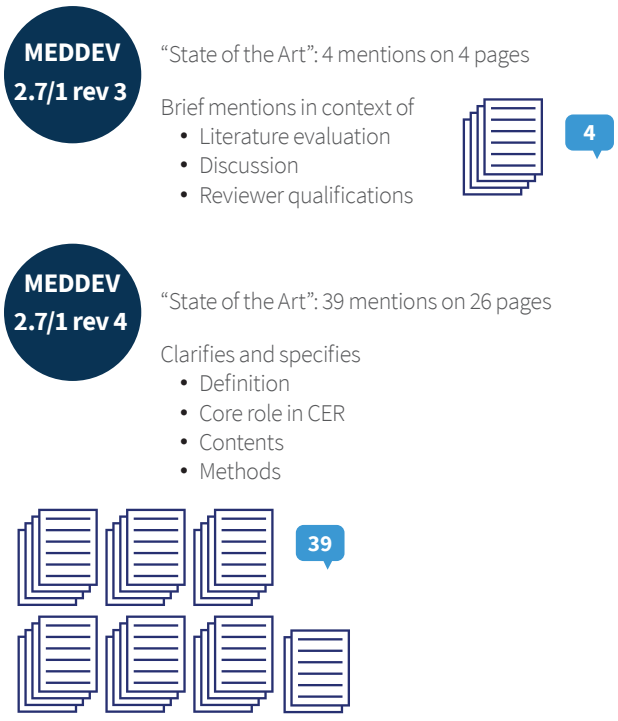
In this whitepaper, we will define what is meant by current knowledge/state of the art in the context of the clinical evaluation,and will provide an overview of requirements and best practices that are MDR compliant, detailed in the MEDDEV 2.7/1 rev 4 guidance. For simplicity, the dual term "current knowledge/state of the art" from MEDDEV 2.7/1 rev 4 will be referred to as "state of the art" throughout this paper.

What is State of the Art?

Prior to MEDDEV 2.7/1 rev 4, guidance referred to state of the art only vaguely. MEDDEV 2.7/1 rev 3 requested the discussion of clinical data "in comparison with" and "taking account of" state of the art, and that the clinical literature data cited "reflect current medical practice and the generally acknowledged state of the art technologies". From a methodological standpoint, this is not much guidance. Thus, methodology, depth, and presentation of the medical background for a device was largely left to one's interpretation, and thus conducted inconsistently, or heterogeneously.

MEDDEV 2.7/1 rev 4 not only clarifies the definition and purpose of establishing state of the art, but also includes guidance on methodology and required content. The revision expands substantially on the four very brief mentions of "state of the art" in the previous guidance (see Figure 1). A total of 39 mentions on 26 pages of the MEDDEV 2.7/1 rev 4 document not only provides a comprehensive understanding of the meaning and significance of state of the art, but also details requirements of how to establish and document this information.

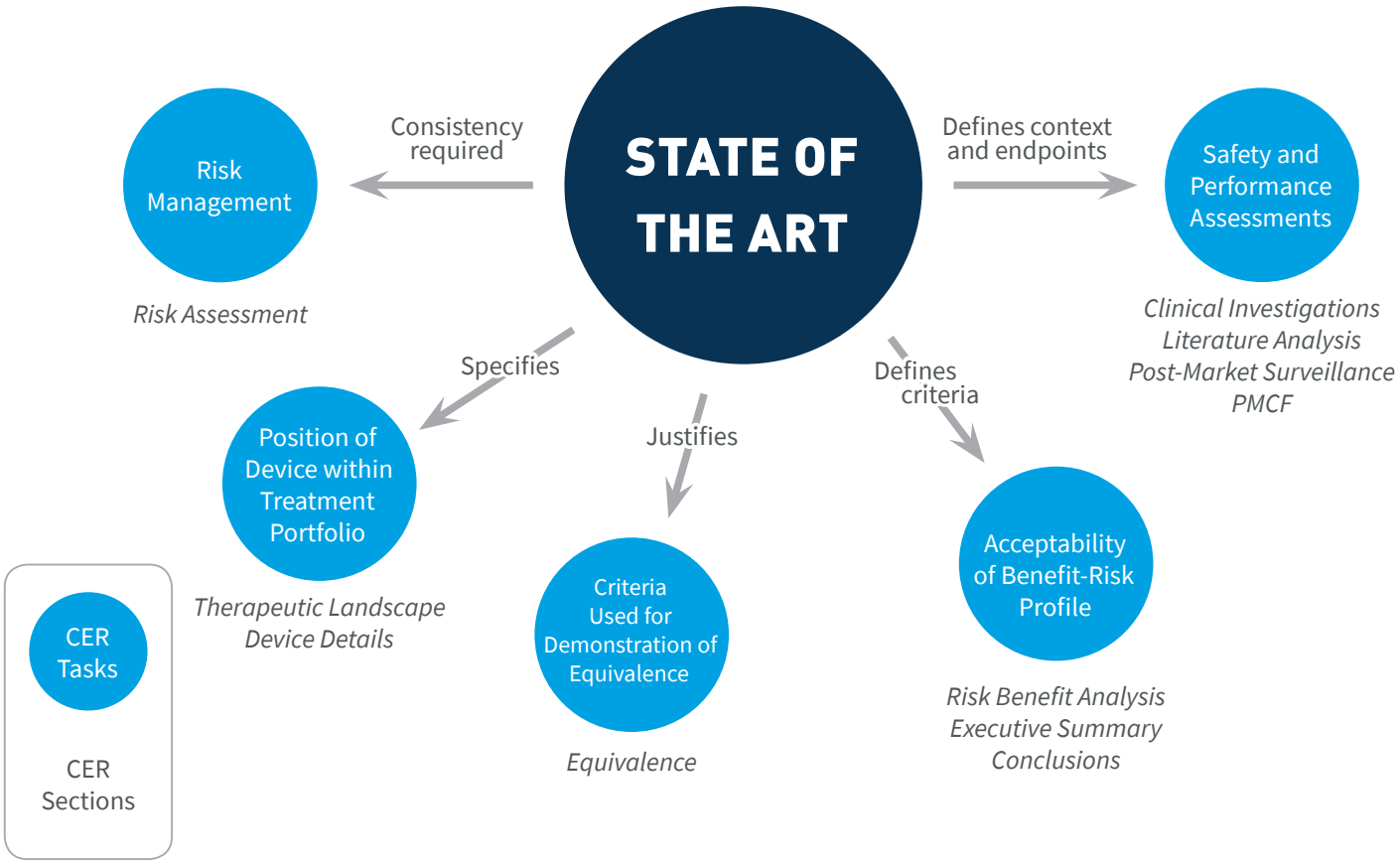
Figure 1: State of the Art in MEDDEV 2.7/1 revision 4



In summary, according to MEDDEV 2.7/1 rev 4, state of the art describes what is currently and generally considered standard of care, or best practice, for the medical condition or treatment for which the device is used. Analysis and description of the state of the art provides the context in which the manufacturer (and Notified Body) can assess the safety and performance of the device, and determine the acceptability of its benefits and risks, in comparison to other available therapeutic options. In the following sections, we will look into the importance of state of the art, and present practical approaches to developing the state of the art in more detail.

Why is it important to establish state of the art during the clinical evaluation?

Figure 2: Core Role of State of the Art



The large number of mentions of state of the art throughout MEDDEV 2.7/1 rev 4 provide not only a comprehensive description of the importance, purpose, and role of establishing the state of the art, but also inform on how to incorporate this analysis into the clinical evaluation.

The MDR stipulates that clinical evaluation planning should include "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" (Annex XIV, Part A, 1).

Figure 2 summarizes several core roles of this analysis. Establishing and describing state of the art is not an isolated task but is central to the entire clinical evaluation. Defining the current, accepted best treatment options, and describing the risks and benefits of these options, provides essential information for multiple aspects of the clinical evaluation, including:

- Assessing safety and performance of a device: selection of endpoints. MEDDEV 2.7/1 rev 4 requires that the clinical evaluation incorporate specific and measurable objectives that are linked to specific safety and performance endpoints. Such endpoints should align with those used in the current therapeutic landscape.

- Assessing safety and performance of a device: data appraisal. Based on MEDDEV 2.7/1 rev 4 clarifications for demonstrating the scientific validity of data presented, it is essential to formulate a clear and methodologically sound plan for the identification, retrieval, appraisal and weighting of clinical data. Appraisal criteria must be consistent with currently accepted scientific standard, and must be justified based on state of the art. The evaluation of clinical data should be done quantitatively in comparison to state of the art, such as by comparing the frequency of side effects or number of incidents.

- Estimating risk and risk management. Data from existing technologies and state of the art therapeutic standards, including risks and benefits of current treatments, should inform risk estimation (for example, hazards due to substances or certain technologies) and approaches to minimize risk.

- Selecting criteria to demonstrate equivalence. Selecting suitable criteria to demonstrate equivalence to another device requires knowledge of current technologies.

- Determining the acceptability of the risk/benefit profile of the device. This must be done in the context of the state of the art, which describes the gold standard (highest level of protection of health and safety) and defines what are considered acceptable risks and side effects, what is considered beneficial, and which duration of effects is considered acceptable.

- Positioning of the device within the available treatment portfolio. This must be clearly defined in a MEDDEV 2.7/1 rev 4 CER. The device should have an improved or at least equivalent benefit-risk ratio compared to available alternatives. However, acceptability can also be justified if the device addresses a significant unmet clinical need or exhibits an acceptable profile in specific situations or patient subgroups.

Thus, establishing state of the art yields information that is essential for determining if the safety and performance of a device is compatible with current standards (in comparison to available treatment options). In other words, state of the art establishes a reference standard that is used throughout the clinical evaluation.

Where should I present the state of the art analysis?

state of the art establishes a reference standard

A recommended approach to incorporate state of the art data into the clinical evaluation is to present this information in a dedicated section of the CER. Such a state of the art section, containing the necessary clinical background information relevant to the CER, can then be referred to and cross-referenced throughout the document.

Multiple sections of the MEDDEV 2.7/1 rev 4 compliant CER need to be supported by state of the art data (see also Figure 2):

- The executive summary should describe the acceptability of the benefit/risk profile in context of that which is state of the art.
- Analysis of clinical data and risk management documentation should address consistency with state of the art.
- Conclusions should address the acceptability of the benefit/risk profile in context of state of the art, and any inconsistencies.
- State of the art justifies the validity of criteria used to demonstrate equivalence.

What should I include in state of the art?

The state of the art section should inform on the clinical background, other devices, medical alternatives, and their safety and performance profiles, based on clinical data. This includes numerical data on safety and performance endpoints against which clinical data obtained

with the device can be compared.
Multiple sections of MEDDEV 2.7/1 rev 4 describe aspects of what content should be provided. A succinct list is given in section 3 of the proposed table of contents of a CER (see Figure 3).

Figure 3: Proposed Example Content for Section 3 Current Knowledge/State of the Art

- *Identify medical fields and relevant medical conditions*
- *Summary and justification of methods used to identify, retrieve, select, and appraise information*
- *Applicable standards and guidance documents*
- *Medical condition*
  - *Description, natural course, consequences*
  - *Clinical forms, stages, severities*
  - *Frequency in general population, by age group, gender, ethnicity, familiar predispositions, genetic aspects*
- *Therapeutic/management/diagnostic options*
  - *Available options*
  - *Historical context, developments*
  - *Summary of advantages/disadvantages of options*
  - *Benefit-risks profiles and acceptability*
  - *Harms*
- *Technologies*
  - *Hazards, risk reduction approaches*
  - *Management of side effects*
- *Users*
- *Diverging opinions of professionals*
- *Unmet clinical needs*

Source: MEDDEV 2.7/1 revision 4 Appendix A9

First of all, the medical field and relevant medical conditions need to be identified, covering all indications and intended patient groups. Next, the methodology used to establish state of the art should be documented and justified, demonstrating objectivity. As much of the data supporting this section will be from published literature, this includes detail on how the literature review was planned and conducted, including sources, search terms, selection criteria, quality control measures, numerical outcomes, and criteria used to appraise the data. Methods should also detail the identification and incorporation of applicable standards and expert documents released by medical associations, particularly, clinical practice guidelines or consensus statements.

A main section of the state of the art is dedicated to the medical condition concerned. This section should cover each relevant condition and describe the condition, its natural course, consequences, and if applicable, different clinical forms or severities. As available, epidemiologic data should be cited to describe the frequency in the general population, and in specific subgroups such as by age or gender.

The central section of the state of the art should present a comprehensive analysis of available therapies for the medical conditions introduced. This section should include the therapy in which the device is used, and available alternatives. It should objectively analyze and present the advantages and disadvantages of the various options, and the acceptability of benefit risk profiles. This section should be supported by the highest quality evidence available in the field, and literature cited should be carefully appraised for scientific validity.

If available, data sources should include current guideline recommendations released by medical associations and the systematic literature reviews conducted to establish these recommendations. This section supports the choice of endpoints that are currently accepted and used in the medical field. The endpoint data cited here will be used as the reference against which device-specific data are compared in the clinical evaluation. Data on safety and performance of benchmark and other devices that constitute the current therapeutic landscape can be incorporated here, or in a subsequent section that informs on the maturity of available technologies. Technological information should include potential hazards associated with technologies, and strategies applied to mitigate these risks.

How do I develop a state of the art section: sound methods?

Because of the breadth of information that needs to be included, developing a state of the art section involves the identification of data for a wide array of topics, from the description of the medical condition, to various treatment approaches, to existing technology.
As for the clinical literature review, it must be demonstrated that sound and objective methods are used to establish the state of the art review, and the data search and selection process must be justified and documented.

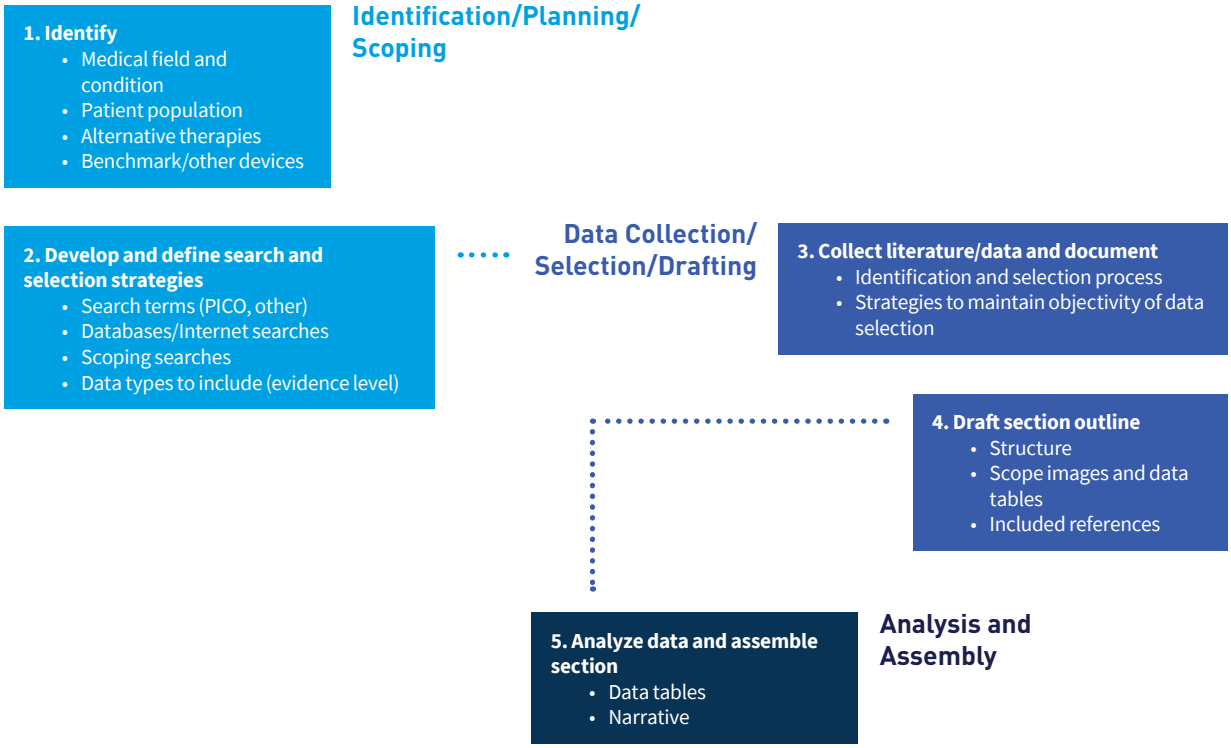
Database searches designed to identify state of the art data/literature are usually broader in scope than those for device-specific clinical literature and will also differ in respect to timeframes of included literature. Thus, separate searches will need to be conducted. Relevant sources of information also include applicable standards and guidance documents, including clinical practice guidelines and consensus statements. Screening citations in scientific literature and clinical practice guidelines represents an important approach to identify relevant literature for the state of the art. Thus, the state of the art literature review is a relatively complex process, and adequate documentation of the identification and selection process may therefore be challenging. As discussed in more detail below (practical example), web-based platforms can help configure, manage, and update the state of the data reviews.

How do I develop a state of the art section: general approach?

When setting out to develop a new state of the art section, there is no one-size-fits-all recipe. However, a general approach/process can be broadly grouped into 3 stages (see Figure 4), which are:

- Identification/planning/scoping
- Data collection/selection/drafting
- Analysis/assembly

Figure 4: Steps to Developing a State of the Art Section



These 3 stages can be further divided into several steps.

Identify key content areas:

At the outset, key content areas for the state of the art review need to be identified and defined. This step is a prerequisite to developing appropriate search and selection strategies. The following should be defined:

- Medical field and relevant medical conditions (include all indications) in which the device is used (per instructions for use)

- Patient population to be treated with the device. This may overlap with medical conditions (i.e., all patients having a specific condition) but may include key contraindications, specific age groups, or specific populations.

- Target therapy, i.e., the therapy in which the device is used. The target therapy may be a specific therapy within a hierarchy of broader therapy descriptions (such as interventional treatment -> surgical treatment-> specific surgical approach in which device is used)

- Alternative therapies. These encompass all alternative therapies available to patients with the medical conditions specified (the patient population). Alternative therapies can include conservative strategies, pharmacological treatment, alternative interventional therapies, or similar interventional therapies.

- Benchmark devices, other devices. Defining state of the art includes describing the current development of the technology(ies) underlying the device, benchmark devices, and other devices that are available and used for the same condition and patient population, and for the same target therapy (in most cases). Data obtained with these devices will be used for comparison with the device in evaluation, and the selection of these devices should be justified in terms of similarities in technology, mechanism of action, materials, and other features.

Develop and define search and selection strategies:

This step is based on the information collected above and includes the following tasks:

- Define search strategies. Using the terms defined above, formulate strategies using systematic search strategies that are objective and non-biased, for example, patient, intervention, control, or outcome queries (PICO). Most likely, multiple searches will need to be performed to cover the diverse aspects needed, and search terms may need to be refined based on scoping searches. Depending on the medical conditions and its frequency and availability of clinical studies and data, search strategies may vary in time periods covered. Furthermore, clinical evidence supporting current treatment standards may accumulate over many years and relevant guidance documents may only be updated periodically. Thus, scoping searches and citation mining (such as of guidelines) are necessary to ensure appropriate time periods searched.

- Identify database sources (databases such as MEDLINE, EMBASE, internet searches) and search engines (PubMed)
- Perform scoping searches
- Based on scoping searches, refine search criteria
- Based on scoping searches, define inclusion and exclusion criteria. For example, for a rare condition, all clinical data from a defined period such as the past 10 years may be included, whereas for frequent conditions, data may need to be limited to higher-level evidence, shorter time periods, or clinical evidence supporting current guideline recommendations.
- Citation mining, i.e. analyzing references cited in other documents (for example, guidelines), is an important means of identifying relevant data for the state of the art and should be considered in the strategies.

Execute searches, retrieve literature:

During this step, searches are performed, results screened, and relevant references retrieved. The following processes are involved and need to be documented/justified:

- Search and selection process. This includes each search protocol (databases, search engine, search criteria, key words) and the corresponding results. Next, the selection process, i.e. inclusion and exclusion of references, with justifications. For example, only a certain level of evidence (randomized studies) may be

included, or only references for a certain time period. As shown below (Best practices when establishing state of the art: challenges), web-based platforms offer one approach to manage references effectively while documenting essential processes.

Step Four

Draft section outline:

In this step, you will determine an outline for the state of the art section, i.e. the logical grouping of the retrieved data. MEDDEV 2.7/1 rev 4 provides guidance regarding suggested content and sequencing (see Figure 3), but, depending on the type of device and availability of data, multiple groupings and structures are possible.

- Using the suggested content for the state of the art section (see Figure 3) as a guideline, group the retrieved references according to the information provided (for example, medical background, epidemiological data, clinical trial data on target therapy, clinical practice guidelines, and data on other devices)
- Determine a logical structure for presentation, starting with main sections, such as medical background, treatment options, and device-specific information (technology). Next, based on the available data, identify relevant sub-categories and determine an optimal structure to present the evidence. How will information on multiple indications be presented, alternating or in sequence? How many alternative therapies will be discussed, and how do they relate (one or several main categories), or multiple therapies within one main umbrella? Sketching out several alternative bulleted outlines with key references can help visualize how to best present the data without confusing the reader.

Step Five

Analysis and assembly:

Once the best possible structure has been determined, the literature needs to be analyzed, appraised, and the individual sections assembled. According to MEDDEV 2.7/1 rev 4, state of the art data serves an indirect supportive role (i.e., not pivotal), and can be generally appraised and weighted for contribution (for example, scientific validity, quality of evidence, and strength of data sets can be discussed in the narrative). For each section and subsection:

1. Analyze the supporting references to determine if additional references need to be included (for instance, reference identified from citation mining) and added to the search and selection process
2. Compile tables. Extract safety and performance outcomes from the state of the art literature into data tables. Depending on data availability and use of endpoints this may involve multiple tables. These tables can be assembled manually, or, as discussed below

(Best practices when establishing state of the art: a practical example—data extraction), be generated using data extraction on web-based platforms. These data tables inform concisely on safety and performance outcomes with available therapeutic options and serve as reference points for the evaluation of device specific data.

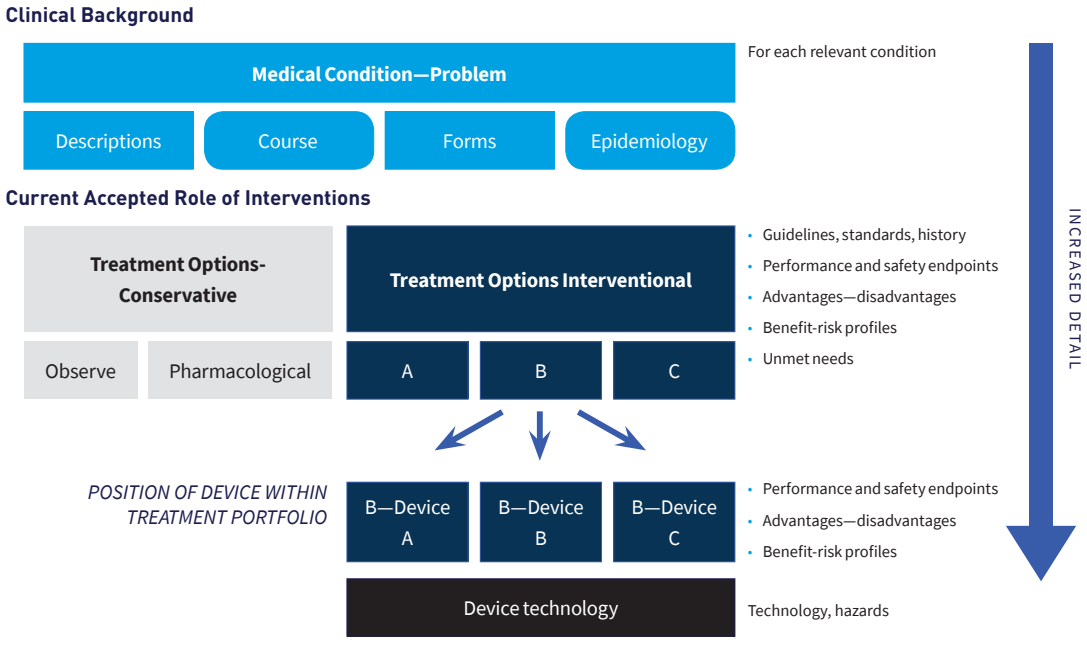
3. Develop the narrative.

Developing the state of the art section: challenges and pitfalls

There is no doubt that establishing state of the art is a challenge. It ranges from key information on the medical condition to a neutral, comprehensive analysis of treatment options, and culminates in a succinct yet comprehensive presentation that defines the currently accepted safety and performance standards against which the device is measured. Not surprisingly, common pitfalls include a perspective that is too broad and inclusion of too much detail, or a perspective that is too narrow, omitting relevant indications and alternative therapeutic options. An important critical aspect of the clinical evaluation that relies on state of the art data is also to appropriately define the position of the device within the currently available treatment portfolio.

To avoid such pitfalls, it can be helpful to develop a conceptual outline or "anatomy" of the state of the art section early during the review (see Step 4 in Figure 4; Figure 5).

Figure 5: Anatomy of a State of the Art Analysis



Best practices when establishing state of the art: challenges

Literature reviews present a number of challenges in general, and even more so when they are being prepared for regulatory compliance purposes.

In order to effectively meet the requirements of the new regulations, it has become increasingly important to adopt a transparent, reproducible process for literature reviews—something that can be difficult to achieve with manual data management or even spreadsheets.

Notified bodies will be looking for documented evidence of the following elements in all CER literature reviews, including those used to establish state of the art.

1

Search Strategy

A well-defined search question provides the foundation for the entire literature review process. If the search is not completed effectively, the quality of everything else in the review suffers. As such, it is essential to ensure that the search question is clear, that the literature search is performed in a systematic fashion, and that the search strategy is well documented.

2

Databases Used

MEDDEV 2.7/1 rev 4 mentions both MEDLINE and Embase, and it is considered best practice to include both of these databases in the search to ensure all potentially relevant literature is located.

3

Search Output

A record should be maintained of all literature returned by the search. This allows Notified Bodies to be confident that all potentially relevant articles were considered for inclusion.

4

Included/Excluded Reference Lists

Not only do the Notified Bodies look for lists of both included and excluded studies, they are increasingly interested in ensuring that the reasons for exclusion are legitimate. Care must be taken to ensure the literature review captures and retains this information for reporting purposes.

5

Appraisal and Weighting of Relevant Studies

MEDDEV 2.7/1 rev 4 represents a significant increase in the level of granularity expected by the Notified Bodies, which also extends to study quality. There are a number of publicly available tools to assess study quality (e.g. SIGN 50, Newcastle Ottawa) and these can be used to capture data such as the appropriateness of the study design, participant selection, measurement of variables, and other indicators of study quality.
Study design is also an important factor to consider, with higher quality studies such as randomized control trials given more weight than other study types.

6

Relevant Study Summaries

Summary data on all of the included studies in your literature review is typically presented in a table format, showing the study type, study design, participants, intervention, and outcome(s).

Common points of failure in state of the art literature reviews

The following are points of failure seen most often in state of the art literature reviews:

1

Incomplete search coverage

With the emphasis on literature reviews in MEDDEV 2.7/1 rev 4, it is reasonable to expect that Notified Bodies will scrutinize them accordingly, starting with the search results. Review groups may choose to narrow their search to reduce the number of references they need to screen, but this can result in missed studies. If any potentially relevant articles are shown to be missing from the results, it can call into question the validity of the entire literature review.

2

Incomplete audit trail

Detailed record keeping is an essential part of the literature review process. Many groups currently use spreadsheets to store and manage the data associated with their reviews. Spreadsheets aren't able to keep track of connections between data and source documents, time stamps, proof of participation, or provide version control. Notified bodies may ask for any or all of this information to verify that the literature review was conducted with a sufficient rigor and adherence to a prescribed process.

3

Ad hoc process

Organizations that adopt and enforce a standard, repeatable process for conducting literature reviews will undoubtedly fare much better in an audit situation. Under MEDDEV 2.7/1 rev 4, the guidance is that the review process must be "systematic". Without a defined and documented process, it may be difficult to produce reviews that meet this standard.

4

Data integrity

Audit failure can happen when the literature review is tainted by small, avoidable mistakes like typos, inconsistencies in data entry, transcription errors, or undocumented manual decisions.

5

Efficiency

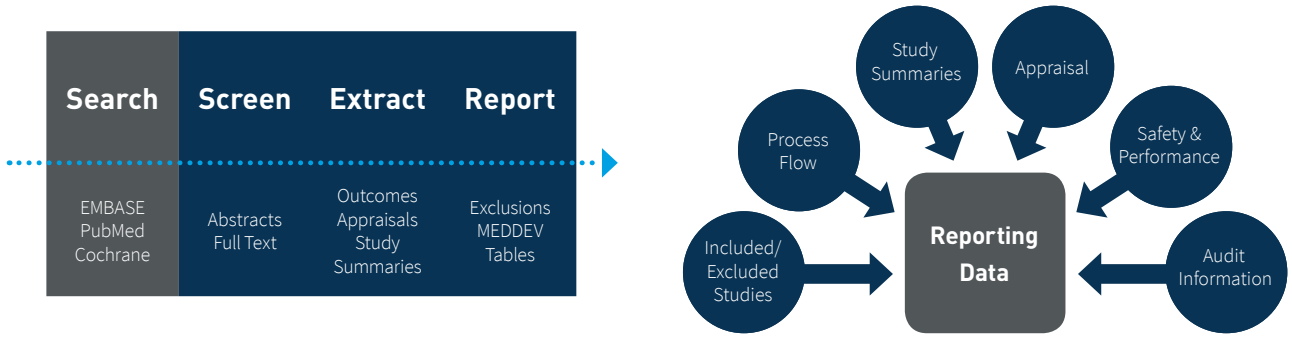
Those involved in conducting literature reviews may also experience a number of efficiency issues related to the following processes:

- Manual data collation
- Manual report preparation
- Difficulty keeping track of articles and data
- Distribution and collection of materials
- Reliable storage of submitted/living reviews

Using DistillerSR for state of the art literature reviews

DistillerSR is a hosted software platform that is used to manage and perform literature reviews in a regulatory compliant, transparent and reproducible fashion. All references, full-text articles and extracted screening, appraisal and study summary data resides within your DistillerSR-based review projects. The software is used to conduct the reviews and to maintain a living dossier of reviews for periodic update.

Figure 6: Literature Review So ware Tools



Best practices when establishing state of the art: a practical example

To illustrate best practices when establishing state of the art, we will use a hypothetical device. The device is the autosuture, a medical instrument used by Starfleet Medical.
The autosuture is:

- A handheld medical instrument used for wound closures.
- Descended from the 20th century suture, and used as early as the 22nd century. By the late 24th century this technology was laser-based (VOY: "The Cloud").
- Function: Seal, close, and promote the healing of wounds from surgery or deep trauma by stimulating the patient's own anabolism. Can be used to close incisions or heal knife wounds beyond the ability of a dermal regenerator.

Formulating search strategies and performing searches

Search strategies to establish state of the art for the autosuture will encompass multiple strategies, including database searches focused on the condition, interventions, history, as well as internet searches to identify applicable guidelines, obtain information on similar competitor devices, etc. To illustrate the use of DistillerSR in this practical example, we will focus on a single search using the PICO method. Applicable keywords would be the following:

- **Patient** – Surgical wound, incision
- **Intervention** – Primary closure, tissue adhesives, adhesives, acrylates, cyoanoacrylates, glue or glues, fibrin-tissue-adhesive, bycrylate, sutur*, surgical stapling, staple, tape
- **Control** – Spontaneous healing
- **Outcome** – dehiscence, infection, cosmetic appearance, patient satisfaction, clinical satisfaction, time for wound closure

Uploading Search Results

Once the research question is defined and the search of relevant databases is completed, the search results can be uploaded into DistillerSR. In the example, 379 references were identified in PubMed.

Figure 7: Importing References to DistillerSR

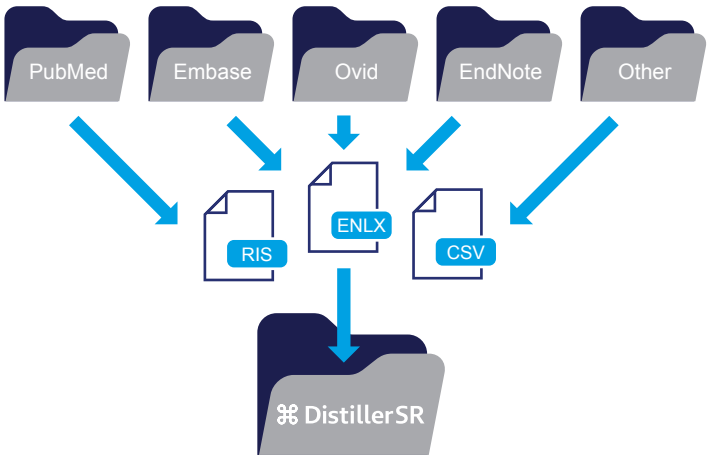
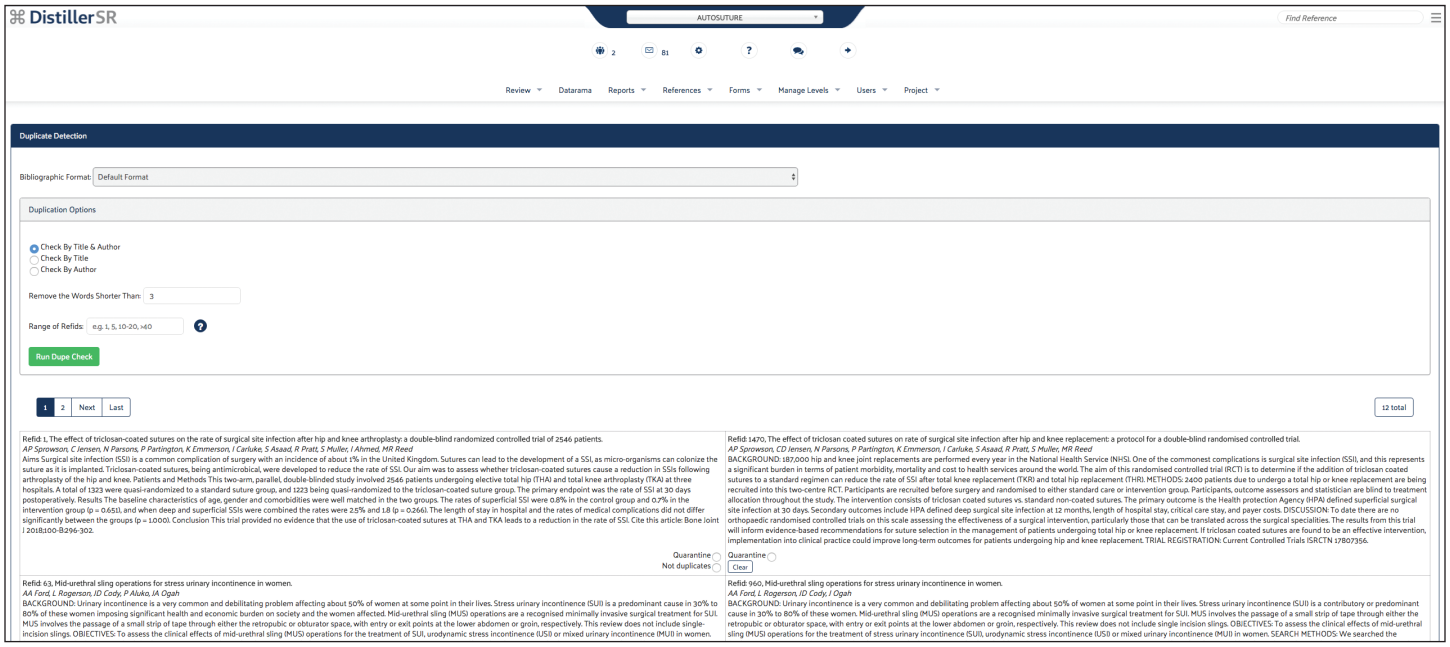


Figure 8: De-duplication of References in DistillerSR

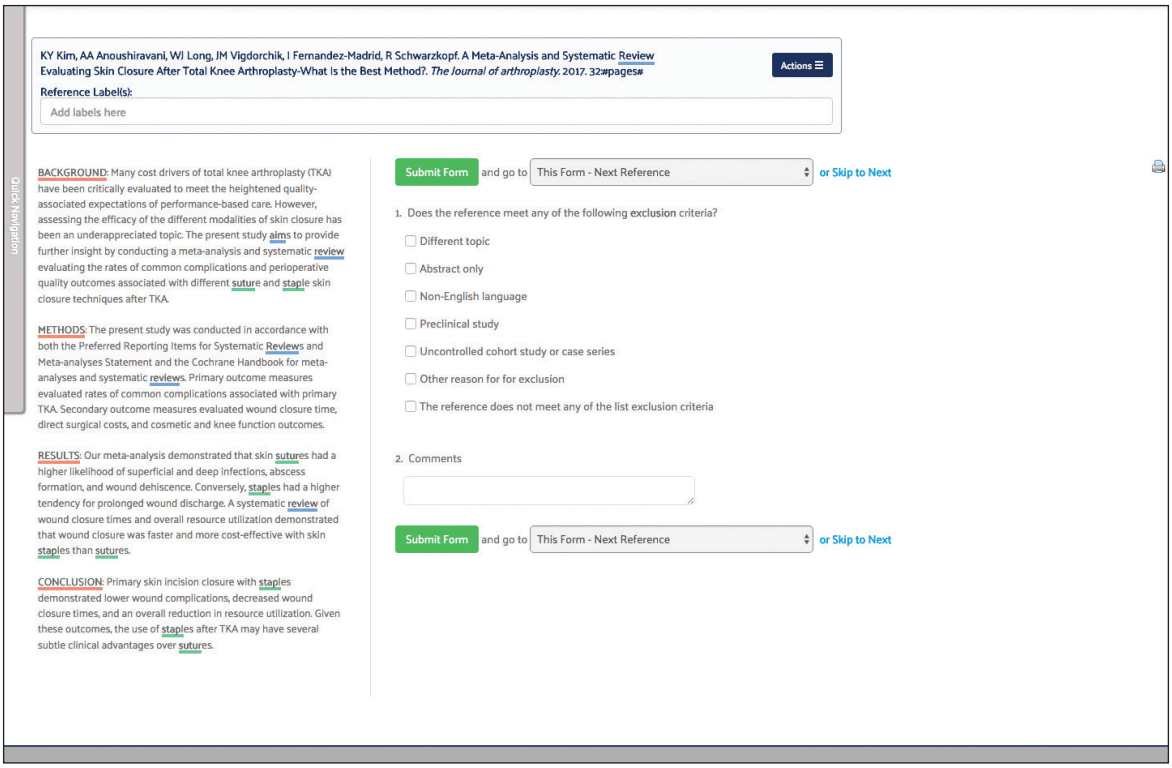


Screening and Article Selection

The first step in processing inbound references is screening them for relevance. This is done using a screening instrument, or form, that asks if the reference contains relevant data. These electronic forms are tailored to the specific domain addressedby the review and they contain questions that determine whether to include or exclude the reference.
One of the main advantages of DistillerSR's electronic forms is that they collect all review data in one place, eliminating the need to manually collate individual responses for processing and analysis.

For this project, the screening form captured study design and patient attributes relevant to the inclusion or exclusion of references from the autosuture state of the art review. Specifically, the form screened for RCTs and systematic reviews and patients with surgical wounds or incisions.

Figure 9: Screening Form for Autosuture State of the Art Literature Review



Reviewers log into DistillerSR and the autosuture review project, view the reference titles and abstracts, and complete the screening forms. When a form is submitted, the data is tagged to the reference and time-stamped along with the reviewer's name so that this information can easily be found and reported on later.

Best practices dictate that two reviewers screen each reference. The software automatically compares answers submitted by different reviewers and identifies any discrepancies or conflicts so that they can be reviewed more closely.

Because this was a regulatory state of the art project, two screeners were used for each reference and the conflict detection tool was used to reach consensus on references where the reviewers initially disagreed.

Once the reviewers have reached consensus to include a reference, it is automatically moved to the next phase of the review. Even when a reference is excluded, however, it is kept on file and the answer(s) that determined it was not relevant are stored with it in case this data is needed to answer the question, "Why was this reference excluded?"

One of the most important things to note about DistillerSR's forms and project workflows is that they are completely customizable to any review protocol. Everything from forms and highlighted keywords to user permissions and task assignments can be configured to create a prescriptive, reproducible process. Once a standard protocol has been established, it can easily be templated and copied for use in future projects. Doing the review in a compliant way, every time, is critical to producing results that will be accepted by the notified bodies.

After initial screening, full text documents associated with included references are typically retrieved and uploaded to DistillerSR for a second round of screening. Screening forms used in second level screening may be the same as those used in initial screening, or can be more elaborate.

In the autosuture project, the team retrieved freely available PDFs from PubMed links and acquired the remaining documents from EMBASE. The screening process was then repeated using the full text documents for references that successfully passed from the initial screening phase.

After full text screening, PRISMA Flow diagrams and included/excluded reference lists may be exported for reporting purposes. The software can also produce reports showing who completed the work, when it was completed and how long each step took.

Figure 10: Complete, Presentation- ready PRISMA Flow Diagrams Can be Produced by DistillerSR with the Click of a Button

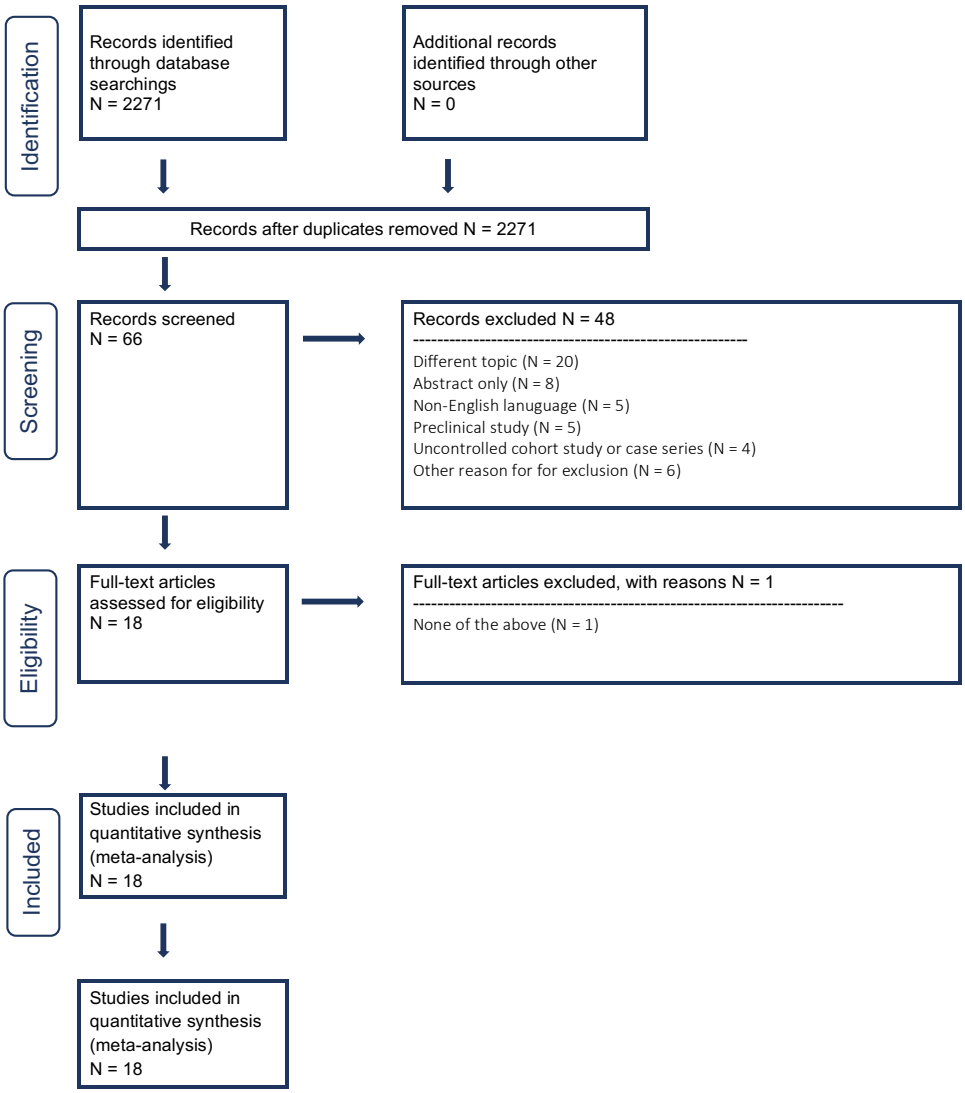
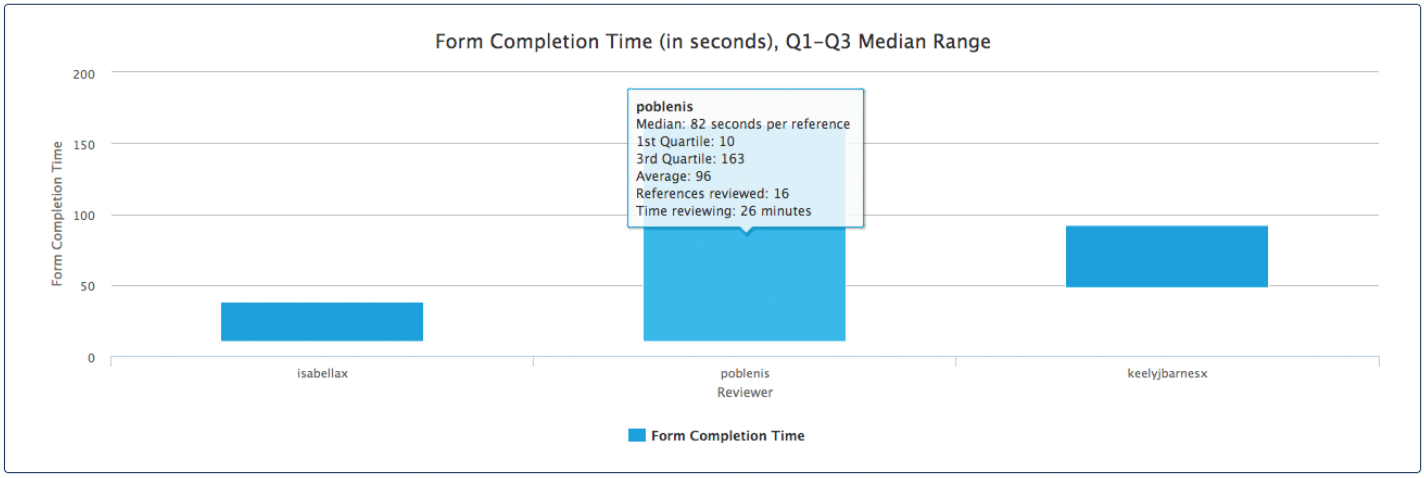


Figure 11: Excluded Study List with Reasons for Exclusion

Result #	Reference	Exclusion Criteria
1	**AP Sprowson, C Jensen, N Parsons, P Partington, K Emmerson, I Carluke, S Asaad, R Pratt, S Muller, I Ahmed, MR Reed**. "The effect of triclosancoated sutures on the rate of surgical site infection after hip and knee arthroplasty: a double-blind randomized controlled trial of 2546 patients.". The bone & joint journal 100-B (2018): #pages#	Different topic
2	**W Ding, Y Tan, W Xue, Y Wang, XZ Xu**. "Comparison of the short-term outcomes between delta-shaped anastomosis and conventional Billroth I anastomosis after laparoscopic distal gastrectomy: A meta-analysis.". Medicine 97 (2018): #pages#	Different topic
3	**H Shakur, D Beaumont, S Pavord, A Gayet-Ageron, K Ker, HA Mousa**. "Antifibrinolytic drugs for treating primary postpartum haemorrhage.". The Cochrane database of systematic reviews 2 (2018): #pages#	Abstract only
4	**N Tachamo, A Donato, B Timilsina, S Nazir, S Lohani, R Dhital, S Basnet**. "Hypercalcemia associated with cosmetic injections: a systematic review.". European journal of endocrinology 178 (2018): #pages#	Different topic
5	**RG Wade, JC Wormald, A Figus**. "Absorbable versus non-absorbable sutures for skin closure after carpal tunnel decompression surgery.". The Cochrane database of systematic reviews 2 (2018): #pages#	Abstract only
7	**DV Chugaev, NN Kornilov, SA Lasunskii**. "[Bidirectional knotless barbed sutures during primary total knee arthroplasty: effective solution or new problem?]". Khirurgiia (): #pages#	Different topic
8	**E Heřmánková, A Žák, L Poláková, R Hobzová, R Hromádka, J Širc**. "Polymeric bile acid sequestrants: Review of design, in vitro binding activities, and hypocholesterolemic effects.". European journal of medicinal chemistry 144 (2018): #pages#	Non-English language
10	**R García-Alva, M Guerrero-Hernández, JE Anaya-Ayala, P Leal-Anaya, A Gabutti, A Picazo, CA Hinojosa**. "Successful Embolization of a Ruptured Ovarian Artery Aneurysm in a Postmenopausal Woman: Case Report and Literature Review of Gonadal Artery Aneurysms.". Vascular and endovascular surgery 52 (2018): #pages#	Different topic
12	**JJ Baker, S Öberg, K Andresen, TW Klausen, J Rosenberg**. "Systematic review and network meta-analysis of methods of mesh fixation during laparoscopic ventral hernia repair.". The British journal of surgery 105 (2018): #pages#	Other reason for for exclusion
13	**S Parisi, C Celletti, M Scarati, M Priora, A Laganà, CL Peroni, F Camerota, G La Torre, D Blow, E Fusaro**. "Neuromuscular taping enhances hand function in patients with systemic sclerosis: a pilot study.". La Clinica terapeutica 168 (): #pages#	Preclinical study
15	**SJ Kim, H Jeon, JH Jung, KM Lee, HY Choi**. "Comparison between over-glasses patching and adhesive patching for children with moderate amblyopia: a prospective randomized clinical trial.". Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie 256 (2018): #pages#	Other reason for for exclusion
18	**AV Gushchin, NV Kadatskaya**. "[Outcomes of intraocular lens implantation in the absence of capsular support: a review of current literature].". Vestnik oftalmologii 133 (): #pages#	Abstract only
20	**T Kim, JC Park**. "Short-term effects of sports taping on navicular height, navicular drop and peak plantar pressure in healthy elite athletes: A within-subject comparison.". Medicine 96 (2017): #pages#	Non-English language
22	**D Kenerson, S Fadeyi, J Liu, M Weriwoh, K Beard, MK Hargreaves**. "Processes in Increasing Participation of African American Women in Cancer Prevention Trials: Development and Pretesting of an Audio-Card.". Journal of health communication 22 (2017): #pages#	Preclinical study
23	**ZY Jia, CG Zhou, JG Xia, LB Zhao, W Zhang, S Liu, HB Shi**. "Endovascular Treatment of 12 Cases of Renal Arteriovenous Malformations: The Experience of 1 Center and an Overview of the Literature.". Vascular and endovascular surgery 52 (2018): #pages#	Different topic
24	**JL Gardy, NJ Loman**. "Towards a genomics-informed, real-time, global pathogen surveillance system.". Nature reviews. Genetics 19 (2018): #pages#	Non-English language
25	**JC Eaton, LL Iannotti**. "Genome-nutrition divergence: evolving understanding of the malnutrition spectrum.". Nutrition reviews 75 (2017): #pages#	Uncontrolled cohort study or case series
26	**A Shpichka, A Koroleva, D Kuznetsova, RI Dmitriev, P Timashev**. "Fabrication and Handling of 3D Scaffolds Based on Polymers and Decellularized Tissues.". Advances in experimental medicine and biology 1035 (2017): #pages#	Other reason for for exclusion
27	**B Adamolekun, L Hiffler**. "A diagnosis and treatment gap for thiamine deficiency disorders in sub-Saharan Africa?". Annals of the New York Academy of Sciences 1408 (2017): #pages#	Abstract only

Figure 12: Performance Metrics



Assessment, Study Summary and Other Data Extracting

Once references have passed through the full screening process they can be assessed for quality, and data relevant to the state of the art review can be extracted. This is done using the same process as screening, but using forms targeted and extracting the data needed to address state of the art.

For the autosuture project, study summary, safety and performance and appraisal forms were used to extract data pertaining to state of the art treatment approaches for surgical incision closure.

Figure 13: Study Summary Data Extraction Form for Autosuture State of the Art Literature Review

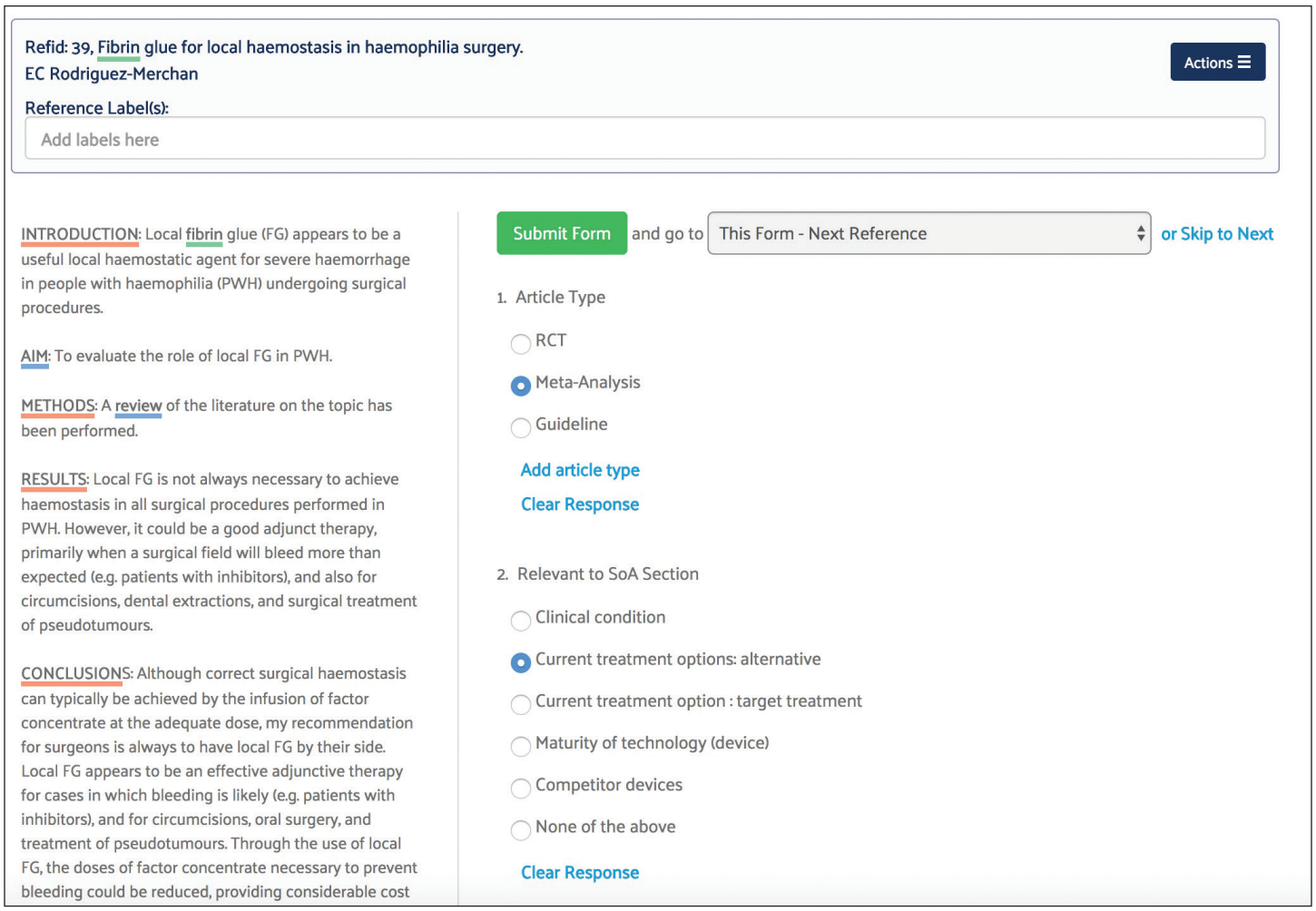


Figure 14: Safety and Performance Data Extraction Form for Autosuture State of the Art Literature Review

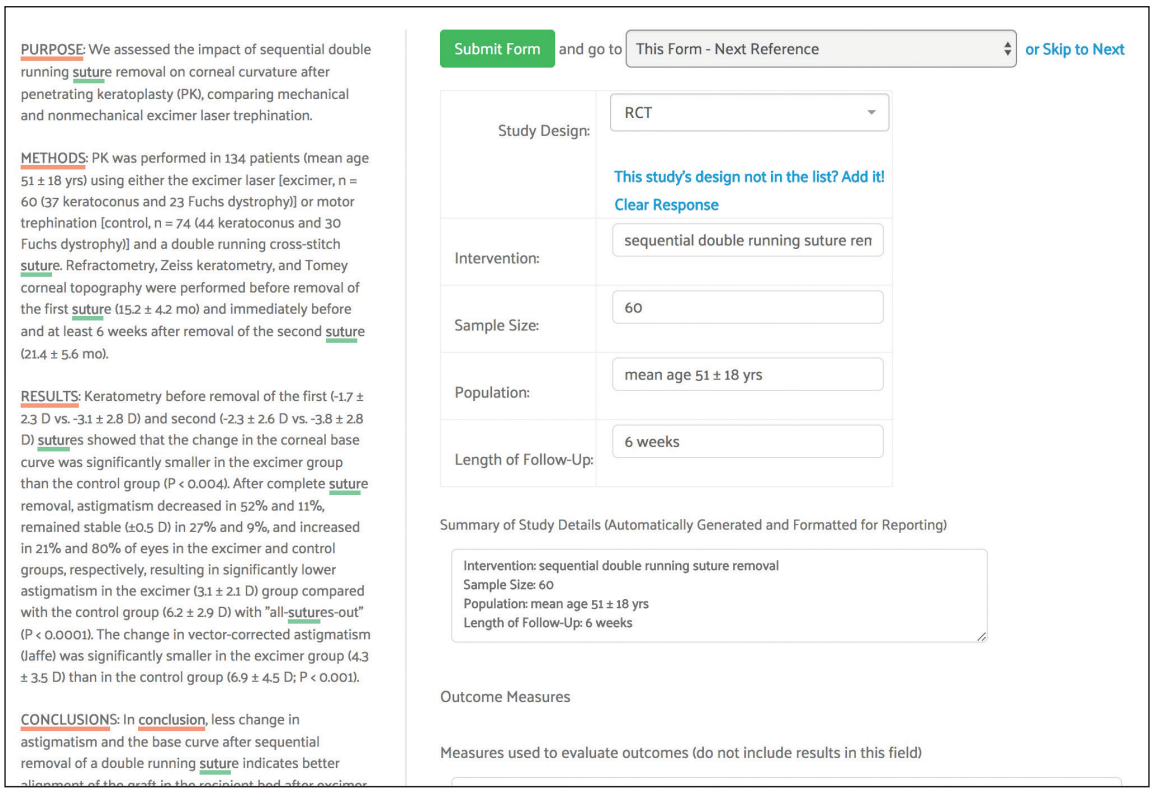
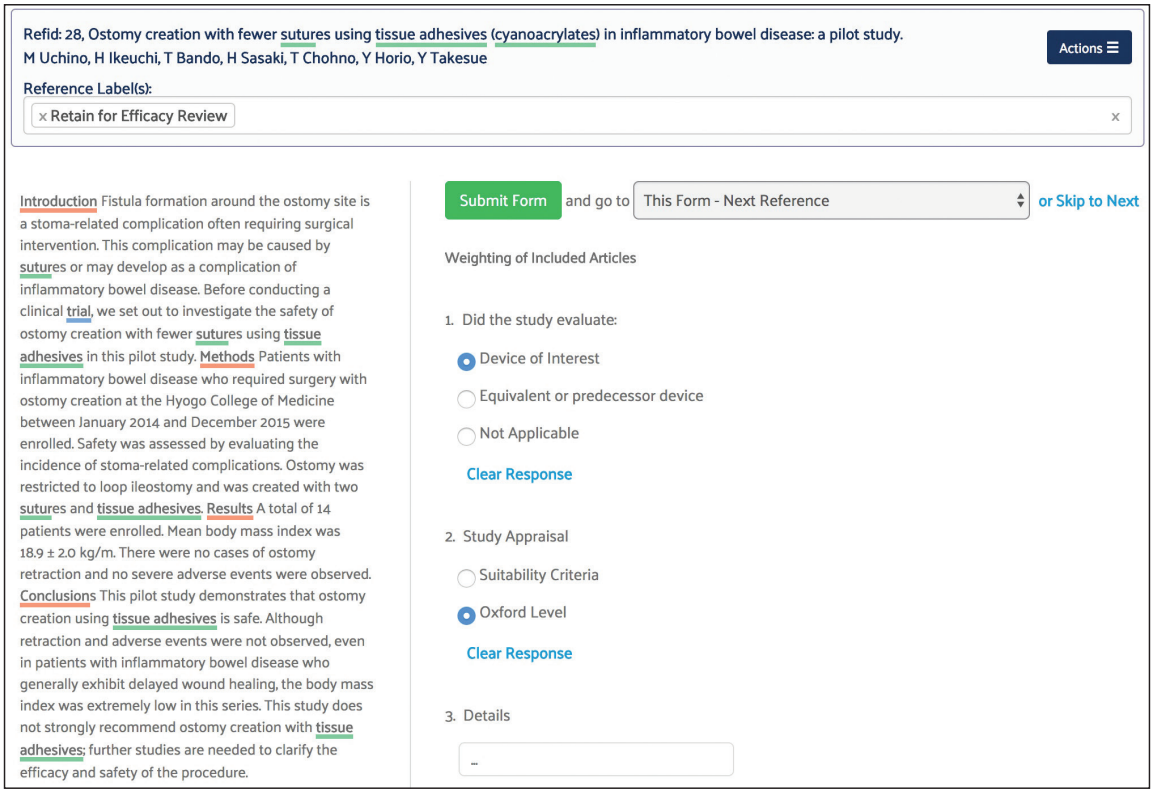


Figure 15: Study Appraisal Form for Autosuture State of the Art Literature Review



Reporting

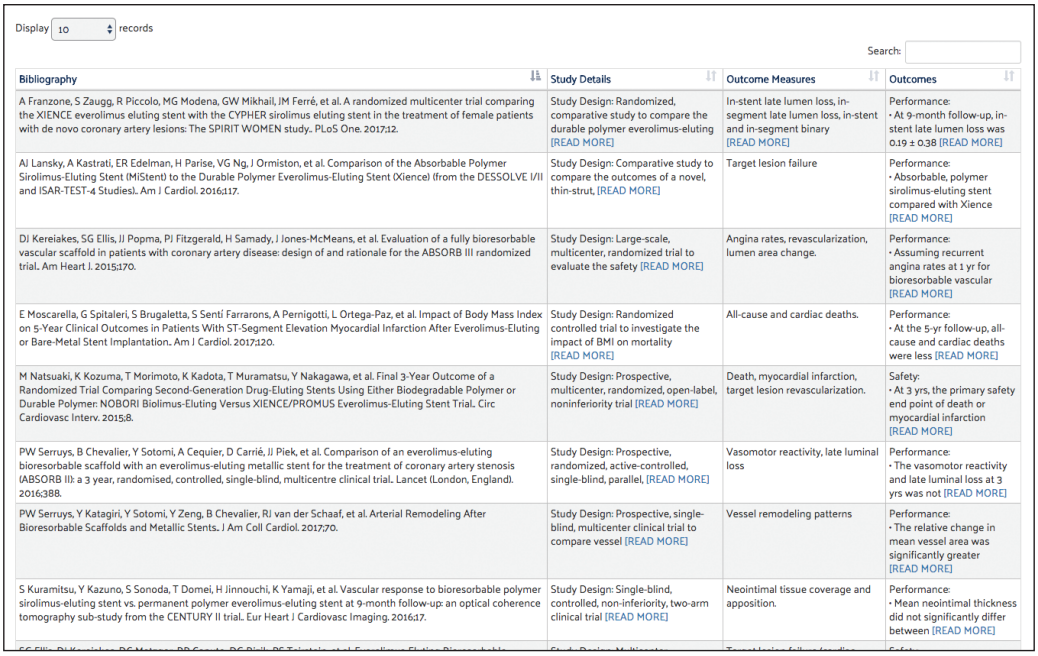
DistillerSR's reporting engine provides a fully transparent view of the literature review process and results. This transparency is essential to demonstrating that a rigorously defined process has been followed to complete the review.
Reports can be generated for direct insertion into an state of the art write up or exported in analysis-ready formats should meta-analysis be required.

Reports can also be customized to capture any subset of the data specific to the state of the art review. Once configured, custom reports can be saved and rerun as new data is added to the review.

Figure 16: Example of a Weighting and Appraisal Table

Bibliography	D	A	P	R	T	O	F	S	C
X Liu, PJ Nelemans, LDS Frenk, H Sengers, SMH Tuinder, PM Steijlen, K Mosterd, NWJ Kelleners-Smeets. Aesthetic outcome and complications of simple interrupted versus running subcuticular sutures in facial surgery: A randomized controlled trial.. *Journal of the American Academy of Dermatology.* 2017. 77	1	1	2	1	1	1	2	1	1
AP Jairam, L Timmermans, HH Eker, REGJM Pierik, D van Klaveren, EW Steyerberg, R Timman, AC van der Ham, I Dawson, JA Charbon, C Schuhmacher, A Mihaljevic, JR Izbicki, P Fikatas, P Knebel, RH Fortelny, GJ Kleinrensink, JF Lange, HJ Jeekel, . Prevention of incisional hernia with prophylactic onlay and sublay mesh reinforcement versus primary suture only in midline laparotomies (PRIMA): 2-year follow-up of a multicentre, double-blind, randomised controlled trial.. *Lancet (London, England).* 2017. 390	1	1	1	1	1	1	1	2	1
HB Cakmak, G Dereli Can, ME Can, N Cagil. A novel graft option after pterygium excision: platelet-rich fibrin for conjunctivoplasty.. *Eye (London, England).* 2017. 31	1	1	2	1	1	1	1	1	2
DW Bartenstein, DL Cummins, GS Rogers. A Prospective, Randomized, Single-Blind Study Comparing Cyanoacrylate Adhesives to Sutures for Wound Closure in Skin Cancer Patients.. *Dermatologic surgery: official publication for American Society for Dermatologic Surgery [et al.].* 2017. 43:	1	1	2	1	1	1	2	2	1
LM Kuroki, MM Mullen, LS Massad, N Wu, J Liu, DG Mutch, MA Powell, AR Hagemann, PH Thaker, CK McCourt, AP Novetsky. Wound Complication Rates After Staples or Suture for Midline Vertical Skin Closure in Obese Women: A Randomized Controlled Trial.. *Obstetrics and gynecology.* 2017. 130	1	1	1	1	1	1	1	2	2
K Bartus, J Podolec, RJ Lee, B Kapelak, J Sadowski, M Bartus, K Oles, P Ceranowicz, R Trabka, R Litwinowicz. Atrial natriuretic peptide and brain natriuretic peptide changes after epicardial percutaneous left atrial appendage suture ligation using LARIAT device.. *Journal of physiology and pharmacology : an official journal of the Polish Physiological Society.* 2017. 68	1	1	1	1	1	1	2	1	1
M Kottmaier, F Bourier, T Reents, A Reiter, M Kornmayer, V Semmler, M Telishevska, K Koch-Büttner, M Deiss, S Brooks, C Grebmer, C Lennerz, C Kolb, G Hessling, I Deisenhofer. Safety and Feasibility of Subcutaneous Purse-String Suture of the Femoral Vein After Electrophysiological Procedures on Uninterrupted Oral Anticoagulation.. *The American journal of cardiology.* 2017. 119	1	1	1	1	1	1	1	1	1

Figure 17: Example of a Study Summary Data Table



Display 10 records

Search:

Bibliography	Study Details	Outcome Measures	Outcomes
A Franzone, S Zaugg, R Piccolo, MG Modena, GW Mikhail, JM Ferré, et al. A randomized multicenter trial comparing the XIENCE everolimus eluting stent with the CYPHER sirolimus eluting stent in the treatment of female patients with de novo coronary artery lesions: The SPIRIT WOMEN study.. PLoS One. 2017;12.	Study Design: Randomized, comparative study to compare the durable polymer everolimus-eluting [READ MORE]	In-stent late lumen loss, in-segment late lumen loss, in-stent and in-segment binary [READ MORE]	Performance: • At 9-month follow-up, in-stent late lumen loss was 0.19 ± 0.38 [READ MORE]
AJ Lansky, A Kastrati, ER Edelman, H Parise, VG Ng, J Ormiston, et al. Comparison of the Absorbable Polymer Sirolimus-Eluting Stent (MiStent) to the Durable Polymer Everolimus-Eluting Stent (Xience) (from the DESSOLVE I/II and ISAR-TEST-4 Studies).. Am J Cardiol. 2016;117.	Study Design: Comparative study to compare the outcomes of a novel, thin-strut, [READ MORE]	Target lesion failure	Performance: • Absorbable, polymer sirolimus-eluting stent compared with Xience [READ MORE]
DJ Kereiakes, SG Ellis, JJ Popma, PJ Fitzgerald, H Samady, J Jones-McMeans, et al. Evaluation of a fully bioresorbable vascular scaffold in patients with coronary artery disease: design of and rationale for the ABSORB III randomized trial.. Am Heart J. 2015;170.	Study Design: Large-scale, multicenter, randomized trial to evaluate the safety [READ MORE]	Angina rates, revascularization, lumen area change.	Performance: • Assuming recurrent angina rates at 1 yr for bioresorbable vascular [READ MORE]
E Moscarella, G Spitaleri, S Brugaletta, S Sentí Farrarons, A Pernigotti, L Ortega-Paz, et al. Impact of Body Mass Index on 5-Year Clinical Outcomes in Patients With ST-Segment Elevation Myocardial Infarction After Everolimus-Eluting or Bare-Metal Stent Implantation.. Am J Cardiol. 2017;120.	Study Design: Randomized controlled trial to investigate the impact of BMI on mortality [READ MORE]	All-cause and cardiac deaths.	Performance: • At the 5-yr follow-up, all-cause and cardiac deaths were less [READ MORE]
M Natsuaki, K Kozuma, T Morimoto, K Kadota, T Muramatsu, Y Nakagawa, et al. Final 3-Year Outcome of a Randomized Trial Comparing Second-Generation Drug-Eluting Stents Using Either Biodegradable Polymer or Durable Polymer: NOBORI Biolimus-Eluting Versus XIENCE/PROMUS Everolimus-Eluting Stent Trial.. Circ Cardiovasc Interv. 2015;8.	Study Design: Prospective, multicenter, randomized, open-label, noninferiority trial [READ MORE]	Death, myocardial infarction, target lesion revascularization.	Safety: • At 3 yrs, the primary safety end point of death or myocardial infarction [READ MORE]
PW Serruys, B Chevalier, Y Sotomi, A Cequier, D Carrié, JJ Piek, et al. Comparison of an everolimus-eluting bioresorbable scaffold with an everolimus-eluting metallic stent for the treatment of coronary artery stenosis (ABSORB II): a 3 year, randomised, controlled, single-blind, multicentre clinical trial.. Lancet (London, England). 2016;388.	Study Design: Prospective, randomized, active-controlled, single-blind, parallel, [READ MORE]	Vasomotor reactivity, late luminal loss	Performance: • The vasomotor reactivity and late luminal loss at 3 yrs was not [READ MORE]
PW Serruys, Y Katagiri, Y Sotomi, Y Zeng, B Chevalier, RJ van der Schaaf, et al. Arterial Remodeling After Bioresorbable Scaffolds and Metallic Stents.. J Am Coll Cardiol. 2017;70.	Study Design: Prospective, single-blind, multicenter clinical trial to compare vessel [READ MORE]	Vessel remodeling patterns	Performance: • The relative change in mean vessel area was significantly greater [READ MORE]
S Kuramitsu, Y Kazuno, S Sonoda, T Domei, H Jinnouchi, K Yamaji, et al. Vascular response to bioresorbable polymer sirolimus-eluting stent vs. permanent polymer everolimus-eluting stent at 9-month follow-up: an optical coherence tomography sub-study from the CENTURY II trial.. Eur Heart J Cardiovasc Imaging. 2016;17.	Study Design: Single-blind, controlled, non-inferiority, two-arm clinical trial [READ MORE]	Neointimal tissue coverage and apposition.	Performance: • Mean neointimal thickness did not significantly differ between [READ MORE]

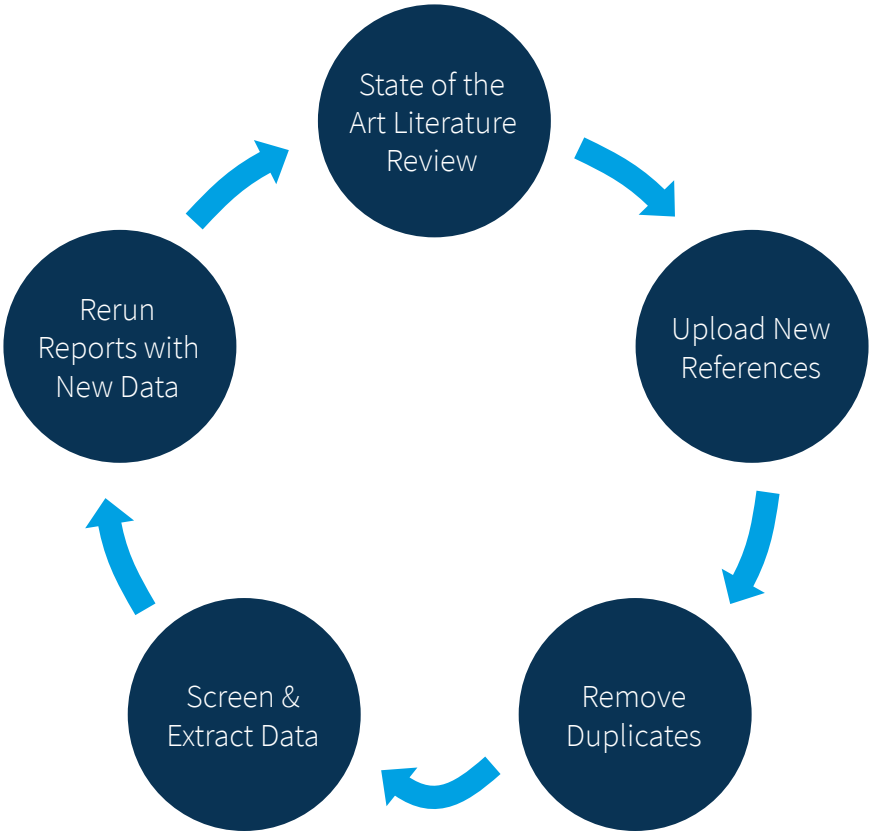
Maintaining Living Reviews

Once complete, state of the art literature reviews can be maintained on the DistillerSR platform in perpetuity and can be periodically updated as new reference material becomes available.

The update process typically involves four steps:

1. Uploading newly located references
2. De-duplication to ensure that references screened in an earlier iteration are automatically removed
3. Screening and data extraction of the new references
4. Producing updated reports to capture new data

Figure 18: Living Review Life Cycle



Summary and Conclusions

Establishing the state of the art is an essential component of a MEDDEV 2.7/1 rev 4 compliant clinical evaluation. This analysis defines the currently accepted safety and performance standards against which the device is measured. A broad range of pertinent information must be identified and presented, ranging from the medical condition and its clinical course, classification, and epidemiology, to a neutral, comprehensive analysis of treatment options, the current gold standard and other available devices. Identification and selection of literature and data pertaining to state of the art must be objective and should not favor the subject device. Thus, documenting thoroughness, standardized processes, and data integrity is imperative. This can be achieved by establishing a systematic approach and by maintaining complete, accurate records of this process using platforms such as DistillerSR.

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HOW CAN WE HELP?

Contact Criterion Edge for a consultation on how we can help you use DistillerSR to develop the state of the art background and maturity of current technology for your device.