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Overview of Clinical Evaluation of the Medical Devices with the Help of Literature Review

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A B S T R A C T

The purpose of this paper is to define the selection criteria and methodology of utilising the literatures for the demonstration with the requirements of the medical device to the applied standards and the claims made by the organisation. The clinical evolution of the medical device is mainly based on the comparison of the information available within the automation with respect to the safety and effectiveness of the medical device so that the collected information shall meet the requirement of the regulatory authority or the applied standards within the framework of design verification and validation activity. This paper is focusing on the elements of utilising the literatures for the review of the literature citation for the clinical evaluation activity. All medical devices sold in Europe must have a Clinical Evaluation Report (CER), and specific and measurable safety and performance endpoints are paramount for an acceptable CER. However, many small medical device manufacturers are struggling to adequately define and subsequently document measurable safety and performance endpoints, especially in the literature review, to support an evidence-based evaluation. Regulations under the old MDR and MEDDEV were not as demanding, and manufacturers are not accustomed to the current systematic process of CER evaluations. Systematic literature reviews (SLRs) are a big part of the CER. The ultimate goal of the CER is to provide sufficient clinical evidence that the device achieves its intended purpose and is safe and effective.

Keywords: Medical, Devices, Regulations, Clinical, Evaluation

1. Introduction

Clinical evaluation report (CER) is a widely accepted document for the approval of medical devices by various regulatory bodies, and literature search plays a pivotal role in drafting a CER.In fact, recent modifications oftheMedDEV 2.7.1 guidelines (June 2016) focused more on the role of literature search as a tool for medical device clinical evaluation and on establishing state-of-the-art treatment of diseases in which the device is used. Hence, in the present article, we discussed errors and challenges in literature search while identifying and appraising evidence (references) and strategies to mitigate them.Clinical evaluation of medical devices is a process similar to synthesizing a systematic review or a researcharticle. Data documentation and publication are the most important aspects ofanyresearch,regardless of whether the outcomes of the research are accepted or challenged. When a documented research is cited as a reference,it assures readers of the quality of the research and presents previous knowledge on the topic under investigation. A reference is important in providing information onpast efforts,
methods, and strategies used;method or strategy alternatives;intellectual property information;and the current status of the selected research topic. Addition of contemporary and historical research data confirms the validity and feasibility of the research project and also reduces the chances of failure, thereby saving cost and resources.For a medical device industry, such addition helps in reducing failures and thus, reduces the cost of development.

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Literaturesearch is acommonly used strategy or amethodof collecting evidenceon a given research question.A precise literature searchnot only provides accurate evidence but also saves time and effortsrequired in collectingevidence. However, unless implemented correctly, literature search can be misleading, time consuming, or useless. Focusing literature search on a precise topic and obtainingrelevantevidencewithin astipulated time often demands high skill levels. Despite several guidance documents and papers on its methodology, the literature search process still has various errors. In order to obtain optimum outcomes with literature search, the analysis of these errors is a high priority study. These errors are related tothevolume of evidence, relevance of the data, tone of evidence, and its value to the research topic. Analyzing these challenges anddevising anaccurate strategy to overcome these would certainly improvise literature search outcomes.

The present article defineserrors due to the incorrect use of key elements during literature search,such as keywords, database, and Boolean logic. We briefly explain how these errorsBmay manifest into either inclusion of noise or exclusion of relevant information. We also explain how these errors can lead to challenges in literature search.Although prima facie, this white paper is focused on literature search for CER and medical devices, it is generally applicable to all types of literature search.

2. Errors

Errors and challenges in literature search are the main reasons why outcomes deviate. Errors have their origin in incorrect use of primary attributes of literature search,viz., keywords, Boolean, and database. The attributes of these errors are stated below:

a. Errors in setting eligibility criteria (type of literature and databases) (type of literature and databases)
b. Errors in selecting keywords and Boolean logics
c. Errors in setting up the search phrases for database

Often, these attributes concur and can form four types of errors:

1. Error of inclusion
2. Error of exclusion
3. Error of inclusive exclusion
4. Error of exclusive inclusion

Error 1– Error of inclusion

The error of inclusion means including more information than required (Figure1).Thiserrormay occur in case of inadequate exclusion criteria, use of broad keywords, non-specific databases, or Boolean logic misuse. In addition, use of improperly formed long search strings,such as several synonyms joined by the “OR” Boolean logic, may resultin the error of inclusion. An error of inclusion may occur even in a topic-specific database if a search phrase contains broad keywords, improper Booleans, or many words with truncations or wildcards.

When an error of inclusion occurs, the overall completion of the task may be delayed because a longtime is required to appraise the literature, while keeping topic relevancy as a prime objective. Furthermore, an error of inclusion leads to high volumes of low value literature,as it returns manyirrelevant results andoften fetches duplicates. Therefore, the effort required in a literature search is disproportionate to the actual usable data obtained and the time taken in the process. However, in case of rare diseases or treatments, the error of exclusion is preferred over the error of exclusion because the target literature remains in the literature pool.

Error 2 – Error of exclusion

In an error of exclusion,relevant data are not included in the search because of an extreme exclusion-driven strategy. This error occurs in three scenarios:

1.When eligibility criteria fail to set correct inclusions

2.Stringent or too specific keywords

3.Use of excluding Boolean logic “AND” or “NAND” to form search strings

Exclusions in the literature can by influenced by literature type, keywords, synonyms, similar words, or phrases, etc. When an error of exclusion occurs, relevant and useful literaturemay be excluded (Figure 2) from the literature. This error can occur even during appraisalowing to stringent appraisal criteria. An error of exclusion may lead to specific literature outputs that often lead to less informationandthusmay cause bias.

Error 3 – Error of inclusive exclusions

Errors of inclusive exclusion by literary quest practitioners are due to distortions. The protocol usually provides a proper set of parameters for exclusion and inclusion in this form of error, but because of selection bias, the key search words used may be related to a particular or preferred (leading) result,

And thus, monotonous data may be returned. MeSH terms or regulated vocabulary for key terms are strongly preferred because these words gather similar information. The discrimination can vary from the inclusion of only good outcomes of a certain medication for a single particulate disorder to the inclusion of specific brand names and case forms only. The quest seems to be inclusive or accurate by the use of multiple synonyms and inclusive boolean logics such as the OR. In choosing and combining keywords, however, biases (including their synonyms and wild cards) lead to errors, and reverse performance and related data can be overlooked (Figure 3). For certain instances, the mistake

Inclusive exclusion often takes place where exclusion conditions are not specified as excluded or promotional literature. This propensity helps to screen data patterns for the supporter. Any of the biases may nevertheless be recognised and discussed in the evaluationMethod.

Error 4 – Error of exclusive inclusions

The fallacy of exclusive inclusion is, as the word implies, related to exclusivity. The key component of this mistake is the use of a particular word or a boolean. Such small contributors to this mistake may be the exclusively specific language accent, geography or exclusively specific exclusion criterion. Extreme caution or critique leads to a mistake in exclusive inclusion which is generally correlated with very precise key words for insufficient Booleans. The quest can also remove keyword synonyms. In this case, the search words are objectively valid and impartial. Thus, the results would include accurate statistics that include good and negative implications with both potential procedures. However, only exact matches are used in the production due to their accuracy and exclusion or minimal logic of connectors. Therefore in some situations where the word itself is an antonym (e.g., ST-highlight MI and non-ST-highlight MI and centered and non-oriented) the term can also be omitted. This technique is helpful if the available data is too big and you want to search very precisely. In other instances, this mistake has similar consequences to the exclusion error.

For example, when looking for non-ST elevations myocardial infarction, "Coronary Artery Disease" AND ("ECG changes" XOR "St elevation") is a particular combination that returns all literature with electrocardiography (ECGs) associated with the coronary artery and excludes ST-elevation in such ECG changes.

3. Challenges

Challenge 1 – Too high data

This is the most frequently encountered literary challenge, especially if the scientist is a novice. The common issue with this form of production is an ambiguous, common, generic and general error in the integration of general databases such as Academy, ResearchGate, or Google Scholar. This challenge, in essence, concerns a large quest. Using the sentence "Event-free Survival" AND "Norfloxacin," for example, returns 4,120 Google scholar results, most of which refer to antibiotics broadly or related medicines other than Norfloxacine from the literature search. This challenge would increase the volume of data and lead to a huge amount of noise and repetition. High volume data makes it difficult to store, tabulate and present. In most cases, during the measurement, three-fourth data from this volume was omitted. Depending on external filers with interest and added importance, about 20 percent of those data are used for citation and comparison in the final documentation.

Challenge 2 – Too low data

This is the second popular difficulty in the science of the literature where the scientist is too detailed and/or has medium-sized experience. The issues with these data are two extremes: if the whole data is analyzed concurrently, the literature review is complete in a short period with no intervention, or because of the difficulties of evaluating the available data the entire procedure is replicated. The common issue with this challenge is that the words, boolean, database or search engine etc. are incorrectly omitted or misused. The use of the data in the final documentation, citation and comparison uses is at first uncertain, relying on additional specific and value-added filters. In certain instances, their reliability and impartial existence remain unclear, even though all data points are analyzed from this method of search.

Challenge 3 – Irrelevant, non-specific data, and noise

Data noise is mostly a problem created by a mistrust of seasoned individuals who work on a new subject, clinical field or procedure. In particular, if a main word has many significances or variations in spelling or is used in more than one area, its use typically contributes to this issue. Specific key terms are typically replaced by non-specific key terms which return meaningless or unspecific data. NexGenTM, for example, is the name of a stent and a knee substitution product. When we search for this in a general database such as Google Scholar, we obtain 2300 results, that include results from knee, stent and hemophilia studies, which are an abundance of irrelevant data for one stent. The use of search phrases such as "Nexgen clinic data" could be a medium strength search phrase prima facie.

Challenge 4 – Non-conclusive search of data

Using very simple words, we often collect term-related information, but the volume or type of information is too limited to justify arguments or draw inferences. For example, when searching 'Widal Test Title 1:80' AND 'Antibiotic therapy in Low Title Enteric Pyrexia,' Google Scholar, Helios, PubMed, Medscape and Medline do not offer any results. However, if any word in the above phrase or phrases are modified, a significant number of ambiguous data is returned to the quest. Only 2 papers can be recovered after the searches have been separated into three parts: "Low Title" AND "Antibiotic Therapy" AND "Widal test." In this case, the data is too descriptive but not enough to make inferences or arguments. Rephrasing the question as "Low Title" AND ("Widal test" AND "Antibiotic") returns 20 articles with relevant antibiotic therapy details, low Widaltitre, and enteric fiber. The evidence gathered cannot be used, however, to reach conclusions outside clinical recommendations and epidemiology. The search results contain substantial noise without any clear details when the query is reframed.

Challenge 5 – Monotonous outcomes – no value addition

When looking for well-established evidence and highly-tested therapies or prevalent illnesses, this challenge is always met. For eg, the term "Aspirin" AND ("Angioplasty" AND "Prophylaxis") returns around 8,200 posts, most of which indicate the need for one-year dual antiplatelet therapy and indefinite usage of aspirin in post-angioplasty treatment. Even if some well-established and generally recognized trials are collected from this search, most data would have the same knowledge, typically repeating the same experiments in various contexts such as different timeframes, subsets, and resources. This form of data lacks added meaning. These details are quoted only once for their better presentation and source.

Challenge 6 – Circular references, cascade of references, hydra-headed, or contradictory results
Hydra-headed findings are often obtained where words are misused and when broad study is done on a disease with the same endpoint and probably different outcomes. Those with limited expertise in literature looking for interventional cardiology can quickly relate to this situation with the dilemma of preference between coronary artery bypass graft and coronary angioplasty, on which various studies are reported, each having different or rather conflicting findings. There was also a related condition of sympathetic denervation and contrast with neuromodulation.Possible correctiveand preventive steps and remedies for improved literature quest.

Challenge 7 – Improper statistical methods:
Examples given focus around 3 scenarios. 1) No corrections over numerous comparisons. 2) Estimates and tests were used depending on those types of distribution data where the distribution was not checked, not plausible or the data was not converted.

Challenge 8 – Lack of adequate controls:
It is possible to cause bias or uncertainty in single-arm trials and other studies that do not have appropriate controls in the following situations: outcomes based on biased outcome evaluations, endpoints subject to normal fluctuations, research with subjects expected to take successful co-interventions, other contributing factors, or where publications suggest variabilities

Challenge 9 – Improper collection of mortality and serious adverse events data:
In cases where mortality studies and other research that could result in serious outcomes, protocols must be in place to "investigate serious patient outcomes, number of subjects lost to follow-up, reasons why subjects leave the study, and the results of sensitivity analysis should be fully reported and published."

Challenge 10 – Misinterpretation by the authors:
Conclusions shall obey the findings section.

Challenge 11 – Illegal activities:
All clinical investigations must be planned, performed and recorded in compliance with EN ISO 14155 or a similar requirement and the Helsinki Declaration.

4. Statistical – Data a Collection and Analysis

When planning a clinical investigation, it is important to consider the potential interpretation of the data and record the analysis strategy, since certain considerations will influence the choice of which variables to gather and probably other aspects of the study design.

4.1 Study population

The study strategy should first assess the population of patients to be used in the main analysis. Documentation is required for all patients who have initiated research procedures and given their informed consent. The content of this medical documentation depends on the individual investigation's comprehensive characteristics, but whenever possible, demographic and baseline statistics should be gathered.
Single arm studies: It is especially relevant for a single-arm trial to explain the result for all patients listed as having the system under review. Thus, even though the device is not used (say for logistical purposes entirely unrelated to the device rather than for medical reasons) full specifics are needed. Intention to treat: 'intention to treat' means that all randomized patients should be included in the study. In other clinical investigations, it offers a cautious approach and also provides forecasts of treatment outcomes that are more likely to mirror those found as the system is placed into operation. Wherever practicable, the protocol can also specify how to resolve any conceivable issues. Any objective admission criterion, calculated before randomization, used to remove patients from analyzes, should be pre-specified and justified. In the case of a randomized study where patients are excluded before randomization, those withdrawals should be reported to enable measurement of the degree to which patients included in the trial constitute a select subgroup of those that may have been included.
The per-protocol population is defined by the following criteria: • completion by the patient of a certain pre-specified minimum exposure to the system concerned
• Availability of key result measures at appropriate and predetermined time (s)
• Lack of significant protocol breaches including infringement of entry requirements. This demographic typically maximizes the potential for a modern device to completely achieve investigative targets.

4.2 Missing values and outliers

Missing principles are a possible cause of bias in clinical trials. Therefore, any attempt should be made to meet all protocol specifications for data collection. Care should be taken when exploring outliers or prominent observation. Clear recognition of a single attribute as an outlier is most persuasive, both medically and scientifically justified. If no protocols for dealing with outliers is used in the investigative protocol, one analysis should be done with the real values and at least another analysis removing or minimizing the outlier effect, and discrepancies should be addressed between their outcomes.

4.3 Estimation, confidence intervals and hypothesis testing

The predictive research strategy should determine the theories to be evaluated and/or the system efficiency characteristics to be calculated to achieve the clinical investigation targets. The mathematical methods for these tasks should be defined for primary (and preferably secondary) variables. Estimates of system characteristics should be followed, whenever possible, by confidence intervals and the way they are measured should be defined.

5. The Conduct and Monitoring Phase

5.1 Changes in inclusion and exclusion criteria

Inclusion and exclusion conditions should, if possible, remain consistent during the recruiting process. This does not always prove feasible in long-term experiments, however. Changes can also emerge from the revelation by testing personnel that frequent breaches of admission requirements exist, or recruiting rates are seriously poor due to over-restrictive criteria. The protocol modification incorporating such improvements should cover any statistical results, such as sample size modifications, resulting from varying case frequencies, or changes to the study schedule. MHRA must be aware of any modifications to these requirements. They must not be enforced before written consensus is reached (see MHRA's paper 'Medical investigations of medical devices – vendor guidance'[4]).

5.2 Checking the design assumption

In larger experiments, the principles underlying the initial design and sample size measurement will typically be tested. This could be especially relevant if the test requirements were made on provisional or unknown details. An intermediate review on blinded data which show that overall reaction, incident rates, or survival experience is not as expected. A updated sample size will then be estimated using suitably modified assumptions which should be justified and reported in protocol adjustment and final report. If such review contributes to the need for a revised sample scale, the MHRA must be notified before any adjustments are made to the number of patients to be included in the clinical investigation and explain the proposed rise.

6. Follow-up and Reporting

The final report should cover both patients and equipment joining the clinical investigation. The grounds for excluding review must be properly recorded. Similarly, with all patients and instruments used in an analysis population, all critical factors must be calculated at all applicable time points.

Additional information on admission screened but not randomized patients can also be summarized. Although it is often difficult to trace all patients involved in the clinical investigation, the sponsor must prove that everything was done in an effort to find patients missing to follow-up. The impact of any patient or data losses, exits from therapy and significant breach of the protocol on the key variables should be carefully considered. Patients lost to follow-up or removed from system usage should be reported and given a detailed analysis, including the explanations for their absence and their care and result relationship.

7. Safety Issues

Clinical studies under the Medical Equipment Directives are not broad enough to identify uncommon harmful effects of devices. Nevertheless, tracking clinical investigations for adverse effects that become evident is critical. These patients should accumulate safety variables as comprehensively as possible.

References of the Applicable Standards

A reference to EN ISO 14155:2011 Clinical investigation of medical devices for human subjects - Good clinical practice (ISO 14155:2011) EN ISO 14155:2011/AC:2011 (The harmonised standard identified by the European Council).

8. Conclusion

The internal auditor's responsibility is to focus on the clinical assessment report's inputs and outputs from the management/organization liability perspective on compliance with all relevant tribute criteria. The internal auditor will verify the accuracy of both input and raw data used to evaluate and conclude the entity.Third-party auditors will have several chances to question the report format, report material, suitability of the methods used, suitability of the information used, accuracy of the information used, competency of the individuals participating in the clinical assessment process.

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