Scientific Evidence in Health Technology Assessment Reports: An In-Depth Analysis of European Assessments on High-Risk Medical Devices

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ABSTRACT

Background: The aim of this study was to examine the scientific evidence on clinical effectiveness and safety used in health technology assessments (HTAs) of high-risk medical devices (MDs) in Europe.

Methods: We applied a systematic approach to identify European institutions involved in HTA and to select reports assessing MDs considered high-risk according to the definition in the new German health care regulation §137h. Reports published between 2010 and 2015 were considered in our subsequent analysis. We used a structured tool based on widely accepted methodologic principles from Drummond’s framework to extract key information on the clinical evidence considered in the reports. Results: Out of 1376 identified reports, 93 were eligible for analysis. All reports based their assessment primarily on direct evidence, in most cases (68%) identified through an independent systematic literature search. In more than half the identified studies considered in the reports, clinical evidence for demonstration of effectiveness and safety was of moderate or low quality. Even when systematic reviews and randomized controlled trials were available for assessment, most studies showed an unclear or high risk of bias. Conclusions: This study confirms that the quality of scientific evidence used in HTA of high-risk MDs is low and therefore the use of evidence needs improvement. The European Commission recently updated the regulation on MDs but mainly focused on the safety of materials and the CE (Conformité Européene [European Conformity]) mark. Our results show that additional changes are necessary, specifically with regard to the marketing authorization process of MDs, with stricter quality requirements based on methodologically robust trials, possibly in combination with other evidence sources.

Keywords: Europe, health technology assessment, medical devices, scientific evidence.

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Introduction

According to the definition by the European Union (EU), a medical device (MD) is defined as “any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of diagnosis, prevention, monitoring, treatment or alleviation of disease” [1].

MDs are generally regulated based on three directives referring to active implantable MDs (90/385EEC), MDs (93/42/EEC), and in vitro MDs (98/8/EC) [2]. Depending on its intended purpose and invasiveness, an MD will be classified as risk class I, IIa, IIb, and III, with class III covering products with the highest risk. For introduction into the European market, MDs need a European Conformity (Conformité Européene [CE]) marking received from an entity that has been accredited by a Member State, a so-called notified body. However, the CE mark does not indicate conformity to a single, predefined standard, nor is it a symbol intended for consumer assurance. It rather acts as a visible sign to let Member State authorities know that the MD is in compliance with the applicable directive(s). Manufacturers must provide evidence that the new device is “substantially equivalent” to a device already on the market. Therefore, obtaining the CE mark does not require a profound demonstration of scientific clinical data relating to effectiveness or safety [3]. Although a subsequent directive (2007/47/EC) as well as a specific guideline (EC MEDDEV 2.7/4) amended the MD 93/42/EEC directive by adding an obligation to generate clinical data for high-risk devices (class III), no detailed information on the requirement of clinical trials was provided [4,5]. This may have contributed to the lack of robust evidence from high-quality clinical trials (e.g., randomized controlled trials [RCTs]) in the premarket stage of MDs [6,7].

When it comes to reimbursement decisions in the postmarket stage, policymakers require clinical evidence to demonstrate

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benefit for patients. One tool to support evidence-informed decision making regarding health technologies, including MDs, is health technology assessment (HTA). HTA is the systematic evaluation of characteristics, effects, and/or impacts of health technology and is conducted by interdisciplinary groups using explicit analytical frameworks that draw from a variety of methods [8]. The results of an HTA are summarized in reports that contain comprehensive information regarding clinical effectiveness and/or cost-effectiveness and may deal with the ethical, legal, and social implications of health technologies for patient health and the health care system [9]. Previous publications have already indicated that HTA agencies face a lack of high-quality clinical evidence when evaluating MDs [7,10]. Therefore, the main objective of this study was to investigate this observation in practice by systematically examining the scientific evidence on clinical effectiveness and safety considered in HTA reports of high-risk MDs in Europe. To our knowledge, this is the first attempt to document the issue on a wide scale. Some institutions provide clear recommendations for policymaking. However, examination of the concluding evidence used for the formulation of policy recommendations was not the purpose of this work.

Materials and Methods

Selection of Institutions and Composition of the HTA Report Pool

Our first step was to follow a comprehensive methodology, as described in Fuchs et al. [11], to identify institutions involved in HTA within European countries. In the second step, we composed a HTA report pool by systematically searching official websites and other online sources (e.g., database of the Centre for Reviews and Dissemination) for publicly available HTA reports published by any of the identified institutions. Reports were included if they focused on an MD (alone or within a procedure), were based on a systematic review methodology, and had been conducted between 2004 and 2015. A more detailed description of the process is given in Fuchs et al. [12]. All included reports were documented in a Microsoft Excel database, and matching documents were downloaded and archived.

In our third and final step, we derived our case sample from this database, applying inclusion and exclusion criteria determined a priori. Specifically, we chose a 5-year time frame to better reflect current practices. Moreover, we included MDs considered high risk in accordance with the new German health care regulation (§137h SGB V). The rationale for choosing this definition is that it provides specific selection criteria for high-risk MDs. Consequently, we included high-risk and highly invasive MDs, if they belong to risk class IIb or III or are active implantable devices. Further specifications determined for the definition of high-risk MDs under this new stipulation refer to devices that 1) interact with essential functions of organs or organ systems, especially the heart, the central circulatory system or the CNS; and 2) are assigned to class IIb and transmitting energy or radioactive radiation [13]. HTA reports on MDs of risk classes below IIb and/or trials that did not match further specifications determined within the stipulation were excluded. We focused our analysis on scientific evidence considered during the assessment of the clinical review (i.e., clinical effectiveness and/or safety) of an MD. Reports that solely relied on the assessment of other aspects (e.g., costs, without consideration of clinical effectiveness and/or safety) were excluded, as the evaluation of these aspects was not within the scope of our study.

Furthermore, we included full-text reports published in German, English, Dutch, French, and Spanish. Reports in other languages, for which only an abstract in English was available, were excluded because for our analysis, we could not rely on abstracts alone for the required information.

A tabular presentation of all relevant inclusion and exclusion criteria used for report selection with respect to the specific case sample is given in Supplementary Table 1.

Data Abstraction

For each HTA report, we extracted key information by using a standardized extraction tool. This was developed on the basis of the methodologic principles to be followed when striving for best practices in national HTA programs, as formulated by Drummond et al. [14], and already used in previous research [10,11]. Specific variables for extraction were defined by following these principles, incorporating our team’s knowledge of and experience in HTA report production. As a result, the tool consisted of three parts, addressing 1) general report variables (e.g., type of report, language, year of publication, etc.); 2) assessment variables (e.g., EUnetHTA core model elements [15]), type of evidence, endpoints, etc.); and 3) variables with respect to decision making (e.g., recommended, not recommended, recommendation with limitations). The full extraction tool is presented in Supplementary Table 2.

As our primary aim was to assess the individual clinical data considered in each HTA report, we focused on the elements referring to scientific evidence. Specifically, we extracted information regarding the following:

- **Evidence base**: This refers to whether the evidence in the HTA reports was primarily based on submissions by the manufacturer, on data identified through an independent systematic literature search, or on both.
- **Type of evidence**: We distinguished between “direct” (e.g., head-to-head trials) and “indirect” evidence. Direct evidence from well-conducted RCTs or a meta-analysis of RCTs is seen as providing the most valid estimates regarding the effectiveness of competing health care interventions. However, in some cases, interventions were not directly compared in RCTs. If there is no or insufficient evidence from direct-comparison trials, results of trials with different comparisons can be used to estimate the effects of treatments [16].
- **Level of evidence (LoE)**: We classified clinical studies used in HTA reports according to the LoEs established by the Cochrane Collaboration [17]. These are summarized in Table 1.
- **Further considerations on scientific evidence**: Whenever possible, we collected the total number of considered studies per HTA report. If HTA reports explicitly evaluated study quality (i.e., risk of bias [RoB]) using a specific tool or approach, such as the Cochrane RoB, Scottish Intercollegiate Guidelines Network (SIGN), or Grading of Recommendations Assessment, Development and Evaluation (GRADE), this information was also considered for analysis. However, an in-depth analysis regarding which RoB assessment tools were used in the HTA reports is outside the scope of this article and will be presented separately. The selection of reports and all extractions were carried out by one researcher and independently checked by another. Discrepancies were discussed and a final data pool was consensitized. Detailed data sheets for report selection and the extractions are available upon request.

Results

Description of the HTA Report Pool

The total HTA report pool consisted of 1237 reports that evaluated 1376 technologies from 33 European institutions and were
دریافت فوری
متن کامل مقاله

امکان دانلود نسخه تمام متن مقالات انگلیسی
امکان دانلود نسخه ترجمه شده مقالات
پذیرش سفارش ترجمه تخصصی
امکان جستجو در آرشیو جامعی از صدها موضوع و هزاران مقاله
امکان دانلود رایگان ۲ صفحه اول هر مقاله
امکان پرداخت اینترنتی با کلیه کارت های عضو شتاب
دانلود فوری مقاله پس از پرداخت آنلاین
پشتیبانی کامل خرید با بهره مندی از سیستم هوشمند رهگیری سفارشات