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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.

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 consented. 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

Table 1 – Level of evidence (LoE) according to the hierarchy by the Cochrane Collaboration [17].

LoE	Study design	Classification of evidence
1a	Evidence obtained from meta-analysis or systematic review of RCTs	High
1b	Evidence obtained from at least one RCT	
2a	Evidence obtained from at least one well-designed controlled study without randomization	Moderate
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study, without randomization	
3	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies, and case studies	Low
4	Evidence obtained from expert committee reports, or opinions and/or clinical experiences of respected authorities	

RCT, randomized controlled trial.

published between 2004 and 2015. Among these 1237 reports, 701 assessed high-risk MDs (≥class IIb). After screening for relevance, 93 reports—of which eight reports were updates—produced by 13 institutions from nine countries, fulfilled our inclusion criteria (see the section "Selection of institutions and composition of HTA report pool") and were considered for analysis (Fig. 1).

Of these 93 assessments, 60% had been conducted in the United Kingdom (UK) (e.g., The National Institute for Health and Care Excellence) or Austria (Ludwig Boltzmann Institute for Health Technology Assessment). Furthermore, 60% of the reports had been published within the last 3 years of the sample period (see Supplementary Figs. 1 and 2). For more details regarding the characteristics of each HTA report, including the corresponding reference, see Supplementary Table 3.

We coded evaluated indications according to the System Organ Classes by the Medical Dictionary for Regulatory Activities [18]. Cardiac disorders were the most frequently evaluated (49 reports [53%]), followed by diseases related to the central circulatory system (36 reports [39%]). Eight reports assessed high-risk MDs applied for diseases of the CNS (9%). All evaluated devices were technologies for therapeutic use. In only three reports (3%), the technologies evaluated also served a diagnostic purpose. The most evaluated group of technologies were implantable devices (e.g., cardiac stents) (62 reports [67%]), which mainly belong to risk class III (37 reports [40%]).

Clinical Evidence in HTA Reports

With respect to the type of the evidence, our results show that all 93 reports based their evaluations on direct evidence. No report clearly stated the (additional) consideration of indirect evidence for assessment.

Among the included reports, the scientific evidence was distributed as follows: two-thirds of the assessments (63 reports [68%]) were based on data identified through an independent literature search. Twenty-nine reports (31%) based their assessment on both an independent systematic literature search and additional submissions of clinical data from the manufacturer. Only one assessment report considered evidence solely on the basis of information provided by the manufacturer.

Our pool of 93 HTA reports included 898 primary studies. When classifying the studies with an LoE of 1a and 1b (high category), studies with an LoE of 2a/2b (moderate category), and LoE class 3/4 (low category) (see Table 1), it was observed that evidence used for MD evaluation consisted mainly of clinical studies ranked moderate to low (551 studies [61%]). Almost half of all studies identified belonged to the lowest evidence category (level 4), primarily represented by case series or reports. Three, five, and seven percent of the studies, referred to studies with a LoE 3, 2b, or 2a, respectively, the majority of which were non-randomized controlled prospective cohort studies (see Figure 2).

The two highest LoE categories were represented by 347 primary studies (39%), which presented evidence obtained from an RCT or a meta-analysis/systematic review of RCTs. However, as Figure 3 shows, most of the RCTs were of moderate to low quality (61% of RCTs in category 1b and 63% of systematic reviews in category 1a), according to the assessment tools applied in the reports (e.g., Cochrane RoB, SIGN, GRADE, etc.).

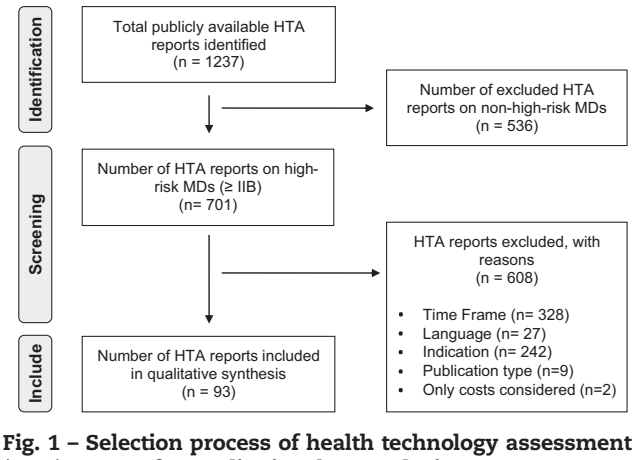

Fig. 1 – Selection process of health technology assessment (HTA) reports for qualitative data analysis.

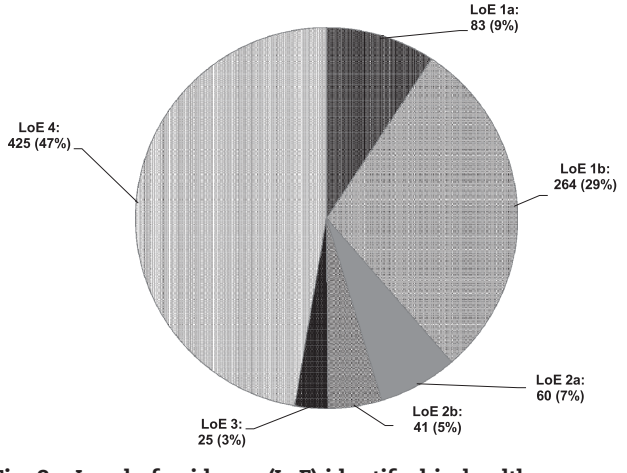

Fig. 2 – Level of evidence (LoE) identified in health technology assessment (HTA) reports.

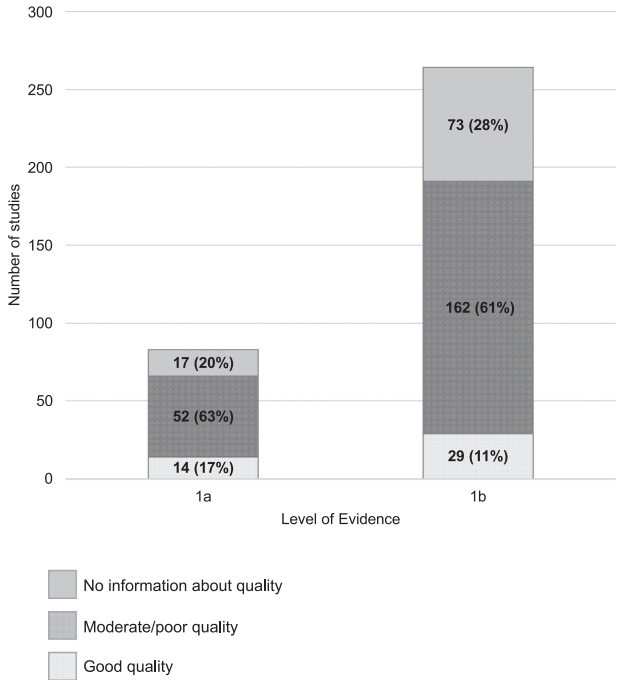

Fig. 3 – Study quality within the category 1a and 1b as documented in included health technology assessment (HTA) reports.

For 17 (20%) systematic reviews and 73 (28%) RCTs, no information about the quality was given or it was deemed not evaluable because of lack of detailed information. Three reports did not provide information about the number of studies or detailed information about the type of evidence. In six reports, no clinical data for assessment of the clinical effectiveness or safety were identified (see Fig. 3).

Discussion

This study systematically analyzed the scientific evidence on postmarket evaluation of MDs by using a tangible basis of existing HTA reports produced by European institutions. The lack of high-quality clinical evidence, which HTA agencies often have to contend with when evaluating high-risk MDs, has been discussed for some time [7,10] and was also noticeable in our study.

Although almost all reports included in this analysis based their evaluation on direct evidence from independent systematic literature searches, good-quality data were scarce. In more than half the reports identified, evidence for the demonstration of the effectiveness and safety came from clinical studies of moderate or low LoE, mainly case series or reports. Additionally, our findings illustrate that even if systematic reviews and RCTs were available for assessment, most of these studies showed an unclear or high RoB according to the specific tools used in their reports. These findings are of great concern because they reflect a tremendous hurdle faced by HTA agencies in their task of making adequate recommendations to health care decision makers. This is particularly problematic with regard to devices associated with significant risks to the patient. The challenge of assessing MDs was also addressed in a recently published retrospective analysis of appraisals of MDs in Austria with regard to other factors (e.g., device risk class, evidence from uncontrolled studies, unmet medical need) that gain importance when making coverage decisions [19]. Those authors found that high-risk MDs with a low LoE, in particular, have favorable odds of obtaining positive, although restricted, reimbursement decisions. This further underlines the difficulties of decision making with regard to coverage for MDs as a consequence of the gap between market approval requirements and evidence needed for the assessment of clinical risk/benefit that is relevant for patients. This evidence gap is a well-known problem and stands in stark contrast to the very strict requirements in the approval process for pharmaceuticals. In Europe and other geographic jurisdictions, it can be largely attributed to the regulation system for market approval. Although MD investigations must adhere to the principles of good clinical practices (GCPs) laid out in EN ISO 14155 [20], there is no legal requirement for valid demonstration of the clinical benefit of a device to obtain CE marking. The main objective of a clinical investigation is to demonstrate the safety and performance (conformity with claims) of an MD. As a consequence, many high-risk devices are granted licensure based on low-quality evidence. Previous research by Rathi et al. [6] showed that high-risk MDs were cleared for the US market on the basis of only two studies on average: one pivotal study (studies that served as the basis of approval by the US Food and Drug Administration [FDA]) and one nonpivotal study. Nonpivotal studies are typically conducted to assess device feasibility, enrolling a limited number of patients to examine the device's performance and to guide premarket development and clinical use.

Following the principle of evidence-based medicine, RCTs are ranked as the gold standard of clinical trials [21]. This is especially true for pharmaceuticals but is increasingly debated within the evaluation process of MDs. In this debate, some researchers argue that RCTs are not suitable for evaluation of MDs because of alleged methodologic issues (e.g., fundamental differences between pharmaceuticals and MDs, complexity of devices, and impossibility of blinding) [22]. However, successful examples, such as the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial showed that high-quality and meaningful RCTs can be conducted for at least some MDs [23]. However, non–RCT-generated data can still be important in the valuation of MDs. A recent report by George et al. [24] set out to explain in what way the National Institute for Health and Care Excellence considers evidence from sources other than RCTs. Specifically, although RCTs remain the preferred and main source of data, the use of non-RCT efficacy data or other clinical evidence is common and necessary for devices (e.g., cochlear implants, insulin pumps, endovascular stents) for which RCTs are, indeed, difficult to conduct or unethical.

Our findings could not confirm the assumption that high-quality studies will occur in the postmarket approval setting and consequently will be available when it comes to decisions on reimbursement.

Additionally, even if a comparative RCT follows a product's launch, the results of the study on relevant outcomes, which are necessary for benefit assessment, may be available only after a considerable amount of time. In such cases, as discussed in the report by Tarricone et al. [25], real-world data can be collected and promptly assessed in the meantime to inform policymakers' decision making. However, such decisions may be of temporary nature, as, for example, in a CED [26].

Policy Implications

We strongly recommend enforcing a requirement of high-quality studies for demonstrating the clinical efficacy and safety of high-risk MDs. Potential methodologic challenges (e.g., blinding) should not preclude RCTs from being carried out (e.g., the

SAMMPRIS trial). However, assessors and decision makers often have to consider study designs other than RCTs. Therefore, we suggest the use of guidelines, such as those from EUnetHTA regarding tools or checklists that are suitable for assessing the RoB in nonrandomized study evidence. The EUnetHTA guideline, for example, recommends the recently developed instrument Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I), previously known as Cochrane Risk Of Bias Assessment Tool for Non-Randomized Studies of Interventions (ACROBAT-NRSI), for adequate evaluation of data quality based on non-RCTs [27,28]. The preference for this tool mainly stems from its advantages, such as the requirement for an endpoint specific assessment, a summary rating, and the availability of more detailed instruction and documentation guides, compared with other tools (e.g., Risk of Bias Assessment tool for Non-Randomized Studies [RoBANS]). ROBINS-I covers seven domains through which bias might be introduced into an NRSI. The first two domains, confounding and selection of participants into the study, address issues before the start of the interventions that are to be compared ("baseline"). The third domain addresses classification of the interventions themselves. The other four domains address issues after the start of interventions (e.g., biases caused by deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result) [29].

Similarly, to further enable HTA agencies to conduct adequate assessments, enhancing transparency and endorsing stricter requirements of reporting by using existing guidelines (e.g., CONSORT statement, or the EUnetHTA pilot core project for Additional Evidence Generation) are crucial [30,31]. This need was also recognized by the European HTA agencies themselves [10].

However, actions at the European level are needed to help contain the risks associated with access to technologies without a robust evidence base. Therefore, we welcome the recently introduced new rules of the European Commission (EC) on MD regulation in Europe. These rules address several issues mentioned in our work [32]. For example, the proposed changes to establish public access of the European Database on Medical Devices will hopefully lead to greater transparency of the European MD market. This database as a central source of information, as well as the planned postmarket surveillance systems, can be expected to improve the overall availability and regulation of clinical evidence [33]. The latter can partially be achieved through postmarket registries, such as the proposed establishment of a "National implants register" in Germany, to obtain (long-term) data on the use, safety, and long-term performance of MDs [34]. Furthermore, the new regulation announces stricter requirements regarding the surveillance of "Notified Bodies" (e.g., employment of well-qualified staff, scheduled and ad hoc controls). Unfortunately, the new EU regulation still falls short. Stricter requirements with regard to evidence on clinical effectiveness and safety of MDs at the time of market entry are necessary to generate appropriate data that enable new MDs to meet the expectations of policymakers in the context of the reimbursement process. As long as this will not change, restrictions or conditions imposed on new MDs need to include an obligation to improve the evidence base, especially in the case of high-risk MDs. As already indicated above, one approach addressing this particular situation is that of the CED, which includes provisional access to novel medical interventions while generating the evidence needed to determine whether unconditional coverage is warranted. Examples of this practice can be found, for instance, in Germany and France [35,36].

However, an ideal approach would combine a degree of premarket evaluation with a degree of probable risk and benefit posed by the device while emphasizing rigorous postmarket assessment in conjunction with carefully planned premarket clinical studies. Two current examples, initiated by the FDA, are the planned establishment of the "National Evaluation System for Health Technology" (NEST) program and the "Medical Device Epidemiology Network Initiative (MDEpiNet)". The NEST program integrates data from clinical registries, electronic health records, and medical billing claims. The MDEpiNet is part of the Epidemiology Research Program at the FDA's Center for Devices and Radiological Health in collaboration with external partners. Both initiatives aim at gathering more comprehensive evidence of the effectiveness and safety of MDs [37,38]. Such new models for evidence generation contain significant potential for reducing the burden of obtaining appropriate evidence across the life cycle of a device.

Strengths and Limitations

The major strength of this study is the thorough and systematic approach taken to identify assessment reports from European HTA agencies. To our knowledge, this is the first review of the scientific evidence considered in publicly available HTA reports assessing high-risk MDs used in Europe.

However, we acknowledge several limitations. Despite the broad set of inclusion criteria, we potentially did not capture all relevant evaluations of the included institutions because of the exclusive reliance on publicly available HTA reports. Although the search for and selection of reports was carried out by two independent reviewers, some reports may have been overlooked. We restricted the selection of HTA reports to those in German, English, French, Spanish, and Dutch, as members of the research team have knowledge of only these languages. Although these comprise 77% of all relevant reports identified, some HTA reports potentially relevant to our analysis may have been excluded. Similarly, some reports in our sample focused exclusively on RCTs, which leaves open the possibility of bias toward this type of study in our findings. Our selection of reports for analysis was based on the definition of high-risk MDs as classified in the new German health care regulation §137h SGB V [13]. Based on the stricter specifications given in this stipulation, compared with the European guidelines for classification of MDs, our case sample might restrict the generalizability of our findings in the area of high-risk devices.

Conclusions

In the EU countries, MDs are essentially regulated in the same way they have been since the 1990s. This means that high-risk MDs can enter the market and be used in humans without the requirement of evidence from robust clinical studies. As a consequence, scientific evidence prior to market approval of high-risk MDs is often based only on evidence from studies that were methodologically inadequate. Our analysis shows that even in the postmarket approval setting, when key players have to make coverage decisions, the quality of the clinical data considered in assessment reports on high-risk devices is still low and needs to be improved. We recognize the need to enforce stricter requirements for high-quality studies for demonstration of clinical effectiveness and safety, possibly in combination with other evidence sources (e.g., registers). The use of guidelines to adequately deal with data quality based on non-RCTs study designs for MD assessment should become common practice. The EU has revised the rules governing MDs, mainly addressing the safety of materials and increasing the requirements for obtaining CE marks. This is a very important advancement with respect to longstanding and controversial issues of the given MD regulation. Nevertheless, the new regulation still lacks requirements for mandatory high-quality evidence on the effectiveness

and safety of MDs for their approval. Innovative evaluation systems at the European or national level (e.g., NEST) that engage all stakeholders could help align interests with regard to device innovation, patient access, and patient safety to drive the development of and more timely access to high-quality, safe, and effective MDs.

Conflict of Interest

BO and MP work for the Federal Joint Committee, which is the highest decision-making body of the joint self-government of physicians, dentists, hospitals, and health insurance funds in Germany. One of its tasks is issuing directives determining the benefit basket of statutory health insurance funds.

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Supplemental Materials

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