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Regulatory and HTA early dialogues in medical devices

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ABSTRACT

Introduction: Specific guidance and examples for health technology assessment (HTA) of medical devices are scarce in medical device development. A more intense dialogue of competent authorities, HTA agencies, and manufacturers may improve evidence base on clinical and cost-effectiveness. Especially as the new Medical Device Regulation requires more clinical evidence.

Methods: We explore the perceptions of manufacturers, competent authorities, and HTA agencies towards such dialogues and investigate how they should be designed to accelerate the translational process from development to patient access using semi-structured interviews. We synthesized the evidence from manufacturers, competent authorities, and HTA agencies from 14 different jurisdictions across Europe.

Results: Eleven HTA agencies, four competent authorities, and eight manufacturers of high-risk devices expressed perceptions on the current situation and the expected development of three types of early dialogues.

Discussion: The MDR has to be taken into account when designing the early dialogue processes. Transferring insights from medicinal product regulation is limited as the regulatory pathways differ substantially.

Conclusion: Early dialogues promise to accelerate the translational process and to provide faster access to innovative medical devices. However, health policy-makers should promote and fully establish regulatory and HTA early dialogues before introducing parallel early dialogues of regulatory, HTA agencies, and manufacturers. For initiating change, the legislator must create the legal basis and set the appropriate incentives for manufacturers.

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1. Introduction

In an environment of ever-increasing healthcare costs, health policy decision makers have a legitimate interest to systematically

evaluate the properties, effects, and impacts of new health technologies by commissioning *Health Technology Assessments (HTA)*. While *HTA for medicinal products* (pharmaceuticals) has been established for over 30 years [1], guidance for *HTA of medical devices (MDs)* is still scarce and heterogeneous [2]. Evidence on the relative benefits and costs of an *MD* (cost-effectiveness), an integral part of *HTA*, is often missing when an *MD* is placed on the market [3]. In recent years, policy makers have introduced a promising approach to improve the evidence base at market entry, i.e., *early dialogues (ED)*. *EDs* are the exchanges between manufacturers and public institutions to obtain guidance on the evidence require-

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ments for regulatory and reimbursement purposes [4]. *EDs* can facilitate the flow of information between manufacturers, *competent authorities (CA)*, and *HTA agencies*. The high relevance of *EDs* for society, industry, and public authorities is reflected by the activities of the European Commission funded EUnetHTA Joint Action 2 [5] and Joint Action 3 [6] as well as the SEED project (Shaping European Early Dialogues for health technologies) [7] that pilot tested different types of *EDs* for medicinal products and medical devices. As a result, manufacturers can obtain non-binding scientific advice using *EDs* of the *European Network for Health Technology Assessment (EUnetHTA)* before starting pivotal clinical trials [8,9].

Awareness of regulatory requirements, such as *HTA*, at an early stage in a product lifecycle, will assist manufacturers in identifying key evidentiary needs and potentially shortening the delay in patient access to life-saving *MDs*. In particular, guidance on study design, accepted clinical endpoints, budget impact, and relative effectiveness help manufacturers address the *HTA agencies'* requirements. The lack of such evidence may delay reimbursement or create an inaccurate perception of the benefits and harms of an *MD*, which usually leads to a denial of reimbursement and a delay in patient access.

This study explores the different perceptions on *EDs* by manufacturers, *CAs*, and *HTA agencies* and investigates how *EDs* should be designed and implemented to accelerate patient access to potentially life-saving and health-improving *MDs*.

2. Regulatory and health technology assessment background

In the context of *medicinal products*, *EDs* are well established and being offered by key *CAs*. For example, the *Innovation Task Force* of the *European Medicines Agency (EMA)* offers informal exchange of information and provides guidance and scientific advice during the product development phase to identify scientific, legal, and regulatory challenges for *medicinal products* [10]. However, the regulatory pathway of *MDs* differs significantly. Therefore, to understand how lessons learned from the use of *EDs* in *medicinal products* can be applied to the context of *MD*, we summarize critical differences in the regulatory pathways between *MDs* and *medicinal products*. To ensure accessibility, we provide definitions of key terminologies in [Table 1](#).

2.1. Medical devices and medicinal products

The regulatory pathway for *MDs* is specified in the *Medical Device Regulation (MDR, EU 2017/745)* [11] while the regulatory pathway for *medicinal products* is detailed in *Community Code Relating to Medicinal Products for Human Use (Directive 2001/83/EC)* [12] and *Regulation (EC) No 726/2004* [13] for the decentralized and the centralized authorization procedures, respectively. The following aspects of the regulations must be taken into account when transferring insights from existing *EDs* of *medicinal products* to *MDs*. First, the levels of involvement by the responsible authorities differ. Manufacturers affirm that their *MD* complies with all applicable legislation by signing the *Declaration of Conformity (DoC)* and affixing the *CE-marking (CE)* [14], without any active involvement from responsible authorities. A *CE-marked MD* can be placed on the market in the 32 countries, i.e., the countries within the *European Economic Area*, *Switzerland*, and *Turkey (CE-region)*. Manufacturers self-certify *MDs* of risk class I, while conformity assessment of higher risk class devices requires the involvement of a *Notified Body (NB)* [15]. The conformity assessment and the self-declaration differs from an assessment by a *CA*. For the latter, *CAs* actively review the evidence provided by a manufacturer and produce a summary opinion to the national authority or the *European Commission (EC)*. Then, the responsible authority forms a legally binding contract with the manufacturer, i.e., a marketing

authorization, which regulates the production, marketing, effective period, and product label. Second, the rigor of the required evidence differs. *MD* manufacturers are not required to conduct randomized controlled trials (*RCTs*) for demonstrating efficacy. In contrast, manufactures of medicinal products must produce evidence on efficacy by conducting *RCTs*. Third, the evaluation of a medicinal product is more complex due to its diverse modes of action, including pharmacological, immunological, or metabolic pathways. Therefore, the evidence generation phase before market entry is substantially longer compared to *MDs*. Despite the fact that evidence generation has become increasingly more complex for novel *MDs*, such as robotics, combination products, or active devices with machine-learning components, evidence based on real-world data is often acceptable. Fourth, the timing of the assessment and the party involved in the discussion differs. Medicinal product manufacturers interact directly with the *CA* during the product development process. *MD* manufacturers, however, interact with private *NBs* to assess conformity and interact for the first time with the *CA* in the post-market phase. This early interaction with official bodies allows informing the manufacturers about *EDs*. *NBs* are public or private conformity assessment bodies that are assessed by an international joint assessment team and designated by the competent authorities (*CAs*) of the Member States [16]. The *NBs* are monitored continuously by the *CAs* who report to the *EC* and to the *Medical Device Coordination Group (MDCG)*.

2.2. Health technology assessment

While the regulations for market access are aligned throughout the *CE-region*, *HTA* requirements differ by country, product type, payer, and place of application [17,18]. From a societal perspective, this decentralized decision-making may be advantageous for accounting for heterogeneous preferences. However, fulfilling such various requirements can be very challenging for manufacturers. Not every *MD* is assessed by a national or regional *HTA agency* and some *HTA agencies* tend to uncritically adopt the decisions of *HTA agencies* in other countries. Due to the plethora of *MDs* (>500,000), many *HTA agencies* only assess the need for an assessment on the initiative of a health committee or a manufacturer after the device has been placed on the market (e.g., see the *NICE* guidance on the selection of technologies [19]). In contrast, for *medicinal products*, *HTA* is mandatory after market entry to obtain reimbursement by the healthcare systems in many countries [20].

2.3. Early dialogues

The utility of *EDs* in supporting regulatory processes is immense from *HTA agencies'* and manufacturers' perspectives. For *HTA agencies*, *EDs* are of importance to identify emerging technologies early, i.e., through *horizon scanning* [21], and to develop methods to assess new technologies. For manufacturers, *EDs* help to maneuver through the regulatory pathway by defining needs, expectations, and requirements for specific patient populations, comparators, endpoints at an early stage, which allows the drafting of efficient *MD* development plans [3]. *EDs* can occur between manufacturers and *competent authorities (CAs)*, i.e., *regulatory EDs*, manufacturers and *HTA agencies*, i.e., *HTA EDs*, or a joint *ED* between manufacturers, *CAs*, and *HTA agencies*, i.e., *parallel EDs* (see [Fig. 1](#)).

3. Methods

To identify whether *EDs* between manufacturers, *CAs*, and *HTA agencies* have the potential to shorten the time to a reimbursement decision and to enable faster patient access, we developed three surveys that we disseminated to experts affiliated with *HTA agencies*, *CAs*, as well as manufacturers of *MDs*. For developing the

Table 1
Definitions of Regulatory Institutions and Processes (in alphabetical order)

CE marking: By affixing the CE-marking to a product, a manufacturer declares that the medical device meets all the legal requirements and that the medical device can be sold throughout the CE region. CE marking does not indicate that a product has been approved as safe by the European Union or by another authority and it does not indicate the origin of a product [35].

Clinical Evaluation Consultation Procedure (Art 54 MDR): For certain class III and class IIb high-risk devices (class III implantable devices and class IIb active devices intended to administer/remove a medicinal product), the Notified Bodies must transmit its clinical evaluation to the Expert Panel before certification of the Medical Device. The Expert Panel has 60 days to provide a scientific opinion to the Notified Body concerning the benefit-risk determination. The Notified Body advises the manufacturer according to the advice of the Expert Panel or the Notified Body provides a full justification where it has not followed the advice [11].

Competent Authority (CA): CAs are the national designated regulatory authorities that are responsible for the implementation of the product and medical device regulations. In most countries, the same regulatory authority is responsible for medicinal products and medical device. The CAs are responsible for granting marketing authorization for medicinal products, for market surveillance as well as for inspections of manufacturers and Notified Bodies [11].

Conformity Assessment: Medical device manufacturers must demonstrate whether the legal requirements relating to a device have been fulfilled by a Conformity Assessment. Manufacturers shall make a self-assessment for low risk devices, i.e., class I devices. For higher risk classes, i.e., classes IIa, IIb, and III, a Notified Body must be involved [11].

Declaration of Conformity (DoC): A medical device manufacturer needs to declare, sign, and continuously update the DoC. It states that all legal requirements have been fulfilled and that the manufacturer takes full responsibility for the product [11].

European Medicines Agency (EMA): The EMA is the responsible agency for coordinating scientific resources for the evaluation, supervision, and pharmacovigilance of medicinal products. The EMA submits their opinion on the granting, variation, suspension or revocation of a marketing authorization to place a medicinal product for human use on the market [13].

Expert Panel (Art 106 MDR): Experts of the panels are appointed by the European Commission in consultation with the Medical Device Coordination Group on the basis of their scientific, technical and clinical expertise. The panels provide assistance to the European Commission, the Medical Device Coordination Group, the Notified Bodies, and the manufacturers regarding the clinical and performance evaluation of certain high-risk medical devices [36].

General Safety and Performance Requirements (GSPR, Annex I MDR): A total of 23 performance and safety requirements must be met for a medical device to be placed on the market. They are set out in Annex I of the MDR. The MDR requires conformity with nine general requirements, thirteen performance, design and manufacturing requirements, and one labeling requirement [11].

Health Technology Assessment (HTA): HTA is a systematic multidisciplinary approach to evaluate clinical, social, economic, organizational, and ethical aspects of health technologies, i.e., medicinal products, MDS, and other health services, in order to inform policy decision-makers [27]. National or regional HTA agencies define HTA methods and recommend reimbursement of a technology.

Marketing Authorization: A marketing authorization allows the authorization holder to place a medicinal product on the market. The marketing authorization is issued by the Competent Authority of a Member State (national authorization) or by the European Commission (centralized authorization for the European Union) [37].

Medical Device (MD): An MD is any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for medical purposes. The manufacturer shall meet and demonstrate the general safety and performance requirements set out in Annex I of the MDR [11].

Medical Device Directive (MDD, 93/42/EEC): The MDD is a European legislative act that is aimed at harmonizing the laws relating to medical devices across the European Member States. The MDD came into force on July 12, 1993 and will be repealed and replaced by the Medical Device Regulation. The directive sets out the goals but the individual European Member States have to devise their own laws to reach these goals [38].

Medical Device Regulation (MDR, EU 2017/745): The MDR is a European legislative act that is aimed at ensuring that safe and performant medical devices are being placed on the EU market whilst supporting innovation. The regulation must be applied in its entirety across the European Member States. The MDR was published on May 5, 2017 and came into force on May 25, 2017. Following the transition period, which has been extended by one year due to COVID-19, the MDR will become fully applicable on May 26, 2021 [11].

Medical Device Coordination Group (MDCG): The MDCG contributes to the development of guidance aimed at ensuring effective and harmonized implementation of the Medical Device Regulation. In addition, it contributes to the development of device standards, of common specifications and of scientific guidelines, including product specific guidelines, on clinical investigation of certain devices in particular implantable devices and class III devices [11].

Medicinal Product: A substance or combination of substances that is intended to treat, prevent or diagnose a disease, or to restore, correct or modify physiological functions by exerting a pharmacological, immunological or metabolic action [12].

Notified Body (NB): A NB is a conformity assessment organization that assesses the conformity of a medical device with the requirements set out in the MDR. Most NBs are private organizations that are designated for certain scopes by Competent Authorities in a joint assessment procedure [11]. The list of NBs and their designated scopes are listed in the New Approach Notified and Designated Organizations (NANDO) Information System.

Placing a Medical Device on the Market (PM): PoM means the first making available of a medical device or medicinal product other than for investigational purposes [39].

Risk classes of Medical Devices: Medical Devices are classified in different risk classes, while class I being the lowest and class III being the highest risk class. Class I devices can be self-certified; all others require the involvement of a Notified Body. The 22 classification rules can be found in Annex VIII of the MDR [11].

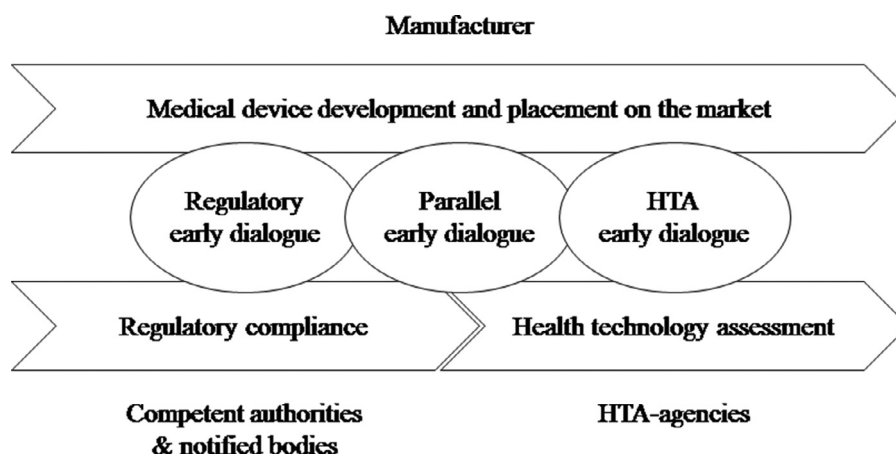


Fig. 1. Types of early dialogues in medical devices

three surveys, we followed the framework for qualitative semi-structured interviews developed by Kallio et al. 2016 [22]. First, we screened the literature to identify differences in the evidence requirements between regulators and HTA agencies as well as differences among HTA agencies in different countries and regions. The results of the literature review provided key areas in which EDs can have a role in shortening the time to reimbursement of innovative MDs. Secondly, based on these insights and a series of discussions among experts within our international consortium, we developed and pilot-tested the questionnaire with key stakeholders from Medtech Europe, the EC's Directorate for the Internal Market, Industry, Entrepreneurship & SMEs (DG GROW), and EUnetHTA. Next, we revised the survey questionnaires based on the feedback. The final version of the surveys systematically explores the current state and the desired characteristics of the three types of EDs, i.e., regulatory, parallel, and HTA EDs (see electronic Appendix). To maximize the generalizability of our survey results, we recruited representatives from manufacturers, HTA agencies, and CAs through Medtech Europe and the network of our project consortium. Specifically, our study participants included CAs and HTAs in 14 European jurisdictions: Denmark, England, France, Germany, Hungary, Italy, Norway, Poland, Scotland, Slovakia, Sweden, Switzerland, The Netherlands, and Wales. As our literature review found that the size of the manufacturer may affect the ability to comply with evidentiary requirements, we selected six multi-national manufacturers and two small and medium-sized enterprises (SMEs) that produce class IIb and/or class III devices that are subject to the clinical evaluation consultation procedure (Art. 54 MDR). We selected the specific MD classes since they necessitate interaction with an expert panel appointed by the EC before declaring conformity. The interviewees obtained the questionnaire in advance by email and were asked to return the pre-filled questionnaire prior to an interview in-person or by phone. The semi-structured interviews were conducted to clarify, verify, and complement the responses to the written surveys. The interviews were conducted by FD, HP, AZ, and CF. All interviewers had at the time of conducting the interviews at least two years of research experience in the field. Then, we transcribed the in-person or telephone interviews, and extracted and analyzed the unstructured information from both the questionnaires and the transcriptions.

4. Results

4.1. Survey and interview respondents

We conducted interviews with eleven of the 14 targeted HTA agencies (79%). Despite several attempts and the use of the consortium's networks of experts, we were unable to recruit respondents from the HTA agencies in Italy, Wales, and Poland. Also, we were only able to obtain responses from the CAs of Hungary, Italy, Switzerland, and the United Kingdom (25% of planned interviews). The interviews were conducted in the period from September 2019 to March 2020 and lasted on average 32 minutes (range: 10–52). Interviewees were decision-makers in CAs, HTA agencies, and manufacturers, including a chief executive officer, market access manager, country director, and director of market access, value, and economics.

4.2. Key insights from HTA agencies

4.2.1. HTA early dialogues

Almost half (5/11) of the HTA agencies have existing programs on ED that are available to manufacturers of MDs. One HTA agency indicated that ED was restricted to first-in-class class IIb and class III MDs addressing unmet medical needs and with a high potential impact on patients. The restrictions are similar to the EU-

netHTA multi-HTA procedure that is designed for medicinal products and MDs [23]. Based on the responses, the ED process typically takes between two to four months and includes teleconferences and face-to-face meetings. One respondent indicated that the HTA agencies do not publish guidelines for EDs on their websites and refer to the briefing book template of EUnetHTA [24] or conduct individual counseling. The HTA EDs focus on the clinical and economic dimensions of an HTA. The main challenge for manufacturers concerns with understanding the required rigor in the design of their study and models for demonstrating clinical- and cost-effectiveness:

"Whether it's more clinical or economic, I'd say it usually covers both, but EDs are both with the caveat that usually the companies have not thought in detail about their models yet." (HTA-11)

Although not all HTA agencies offer EDs, more than 70% of our respondents recognized the utility of EDs in enhancing the evidence base used to inform reimbursement decisions. However, two agencies mentioned the lack of experience as a perceived barrier to the adoption of ED by HTA agencies and manufacturers.

Lack of capacity or willingness to engage in early dialogue: Medtech is yet to learn from pharma and biotech. (HTA-5)

Also, countries with smaller market size saw benefits in organizing HTA EDs at the international level:

"[Market size] is why it makes sense for us [small country] to participate in EUnetHTA collaboration because we can make these assessments together and have more impact from the point of view of manufacturers." (HTA-1)

Eight of the HTA agencies argue that the HTA EDs should be carried out shortly before or after the product is placed on the market. An HTA ED before the product is placed on the market can minimize the risk that a technology that is not eligible for reimbursement is developed to a commercially viable product. One HTA agency highlights the importance of the timing of EDs on clinical and economic evidence:

"For advice on the clinical study design, interactions need to be early. For advice on health economic modelling etc., it is probably better to interact when a bit more knowledge is available (especially the price)." (HTA-7)

4.2.2. Parallel early dialogues

Seven of the eleven HTA agencies explicitly indicated that they are interested in expanding the scope of cooperation with the CAs, while the remainders saw at least a potential in such cooperation in a limited form. Almost 50% of HTA agencies in our sample reported that the exchange with the CAs is too infrequent (less than 2–3 times a year) and not formalized. Five of the HTA agencies expect that parallel EDs will accelerate patient access to device technologies especially due to better quality of data for the assessment; the remainder was inconclusive as there is little evidence and immature processes:

"It depends on the timeliness of the organization, how fast EDs are conducted and how many technologies need to go through an early dialogue process. In [our country] they have been behind in the discussion of prioritization, so the process is still immature." (HTA-1)

Eight HTA agencies identified the joint evidence generation of regulatory and HTA evidence as key to increase efficiency, especially in economic evaluation, valuation, market access, and financing of innovative and advanced MDs. HTA agencies recognized the complexity of the process, particularly related to the type of stakeholders involved in the process. Seven HTA agencies identified healthcare professionals as key stakeholders. The majority of the HTA agencies believed that clinical experts, health economic experts, and patient representatives play important roles in the discussion:

"We may wish to have all stakeholders at the table in all phases of the innovation process. But it is hardly feasible. Instead, it seems

plausible to expect from NBs to require patients' perspectives and costs perspectives in some pilot projects." (HTA-5)

In addition, our respondents highlighted the following challenges as barriers to a successful implementation of parallel EDs: the heterogeneity of MDs (e.g., diagnostic, implantable, or software devices), the lack of uniform national or international HTA methods, and the lack of financial and personnel resources.

4.3. Key insights from competent authorities

In general, CA does not have any statutory mandate for conducting consultation as prescribed by the MDR or national legislations. This absence of mandate is consistent with the principle that advising and auditing manufacturers would violate the impartiality of the audit process itself [25,26].

"Because of its role as a competent authority and in order to prevent conflicts of interest, CA-2 does not, in principle, offer advice. [...] As there is no legal basis for this, no such exchange is planned for the future." (CA-2)

CAs are not directly involved in the *conformity assessment*, i.e., they only conduct post-market surveillance. The CAs of other member states can influence the certification processes through the MDCG, which is composed of representatives from the CAs of member states. The main role of the MDCG is to advise and assist the EC and the Member States in ensuring a harmonized implementation of the MDR.

4.3.1. Regulatory Early Dialogues

None of the CAs in our study formally offers regulatory EDs. However, one CA offers the possibility of an informal interaction when requested by manufacturers. CAs consider such requests as valuable for the following reasons. First, they can obtain information about emerging innovative technologies prior to market placement. Second, they can develop new guidance together with the manufacturers to address previously unforeseen regulatory needs.

"We welcome approaches from our stakeholders [...]. This particularly helps new innovations, where understanding the regulatory process may be a challenge. (CA-4)

Nevertheless, the authorities suggested that the manufacturers' lack of motivation to interact was an obstacle.

"Engaging with regulators can be perceived as risky by some in industry – some feel it may lead to increased burden." (CA-4)

4.3.2. Parallel early dialogues

Parallel EDs exist in two countries, Hungary and the United Kingdom, as indicated by the CAs in our survey. Both parallel ED programs have a non-MD focus. One CA, however, includes software products, which are technically MDs and regulated by the MDR.

"Currently the agency has such collaboration in place for advanced therapy medicinal products (ATMPs) and is looking to have similar arrangements for software devices. There is nothing on MDs at the moment." (CA-4)

4.4. Key insights from manufacturers

All manufacturers indicated that they focus on different aspects of HTA during the different stages of a product lifecycle. Depending on the regulations on the safety and performance, and the national HTA requirements, clinical evidence is usually addressed at least one year before a *conformity assessment*. In contrast, requirements on economic endpoints are typically fulfilled after market placement.

"[It]depends on the stage when the HTA-evidence is collected. We start [with clinical endpoints], then in some countries, we may explore comparative effectiveness data, including quality of life (QOL) and

patient-reported outcomes. The economic aspects come later. [...] Economic evidence is collected basically after the CE-marking." (MANU-4)

The HTA requirements (provision of evidence on clinical endpoints, cost-and cost-effectiveness studies, and appraisal of ethical, social, and legal aspects [27]), and, therefore, barriers to market access, differ by country.

"For Germany, there is no hurdle as of today because so far, HTA has never been a barrier, but the situation is evolving rapidly. In France, it is clearly an obstacle because if you do not have a positive HTA, the product cannot be marketed at all. For Italy, it is sometimes a hurdle because there are some regional health systems that do HTAs. So it really depends on the context, although at the national level [in Italy], HTA has no relevance." (MANU-4)

4.4.1. HTA early dialogues

Half of the manufacturers interviewed are aware of the existence of an HTA ED. However, only two were familiar with the HTA ED initiatives of their target markets' HTA agencies. Only one respondent knows about the HTA ED initiative of EUnetHTA. The manufacturers cited the following reasons for the lack of awareness: resource constraints on both sides (manufacturers and HTA agencies) as well as poor protection of intellectual property. The perception of weak protection of intellectual property seems to persist although involved parties have to sign confidentiality agreements in all EUnetHTA EDs [28].

"There are several internal hurdles: capacity, the problem of confidentiality as MDs are less protected than drugs." (MANU-2)

To optimize the benefits of an ED, manufacturers expect that an ED follows a structured and transparent process and has the potential to reduce uncertainty in the evidence requirements and its use to inform regulatory decisions.

"The ED can provide useful insights to manufacturers as to what are the most important parameters for HTA to collect. So, it can be a fruitful dialogue for both manufacturers and HTA bodies. The potential utility of EDs for manufacturers may even increase in the future." (MANU-4)

A majority of manufacturers emphasized the importance of having an ED early, at least one year prior to declaring conformity. All agreed that the ED should be a continuous process, not a one-off discussion.

4.4.2. Parallel early dialogues

Four manufacturers recognized potentials in the utility of parallel EDs since both CAs and HTA agencies have overlapping requirements, particularly in the generation of clinical evidence. Moreover, they expect to realize the largest efficiency gains in reducing the uncertainty in evidence requirements for complex MDs.

"[We expect from parallel EDs] to get some guidance on how to streamline the evidence strategy/plan with fulfilling the regulations." (MANU-8)

Half of the manufacturers saw the greatest challenges of parallel EDs on the side of the CAs and HTA agencies, mostly due to the different fields of expertise. In addition, the relevant authorities are based in different countries that may have different preferences on the provision of care, thereby resulting in different evidence requirements for reimbursement decisions. Therefore, the manufacturers expected a lack of aligned recommendations from CAs and HTA agencies.

"[...] I see big limits as the capacity of HTA bodies to dialogue with the regulatory process as defined by the MDR. The regulatory and HTA processes are managed by types of subjects that are completely different." (MANU-4)

According to four manufacturers, a parallel ED should be conducted approximately a year before entering the market and potentially earlier if a clinical study is required. The manufacturers prefer to have multiple meetings as new questions arise constantly

in the regulatory and reimbursement processes. Three manufacturers regarded CAs and NBs and one manufacturer regarded the regional authority as critical dialogue partners. From manufacturers' perspectives, healthcare professionals, clinical experts, and health economic experts should be involved in a dialogue according to five, seven, and six manufacturers, respectively. Patient representatives were deemed to be the least relevant (indicated by only four manufacturers).

5. Discussion

This study explored the extent to which EDs between manufacturers, CAs, and HTA agencies have the potential to shorten the time to a reimbursement decision and to enable faster patient access to innovative technologies in Europe. However, we have to recognize that CAs and HTA agencies have different competences: while CAs are specialists in assessing and balancing benefits and risks, HTA agencies have expertise in effectiveness and safety as a starting point to assess cost-effectiveness. The benefits of *parallel EDs* may lay in finding an agreement, e.g., on clinical endpoints, relevant for both processes [29]. For deriving long-term policy recommendations, the regulatory environment needs to be changed. Some experts are convinced that the certification process should be regulated centrally at a supranational level [30]. The importance of such a process is even more pronounced after the implementation of the new MDR, which limits country-specific mandates. Second, a *conformity assessment* is a private sector process without involving public authorities. The roles of CAs become prominent after market access, i.e., post-market surveillance. The *clinical evaluation consultation procedure* (Art 54 MDR) is the only exception where authorities learn about a new product through official channels before market placement. For devices classified as high-risk (see Table 1), NBs have to submit a clinical evaluation to an *Expert Panel* that is appointed by the EC. However, even in this case, the product development is very likely to be at a very advanced stage, i.e., the clinical evidence may already be available. Moreover, the confidentiality obligations (Art 109 MDR) does not allow CAs or NBs to initiate an HTA ED as all parties involved in the regulatory process should respect the confidentiality of commercially relevant information. Third, deciding whether to reimburse an MD is a highly decentralized process that varies considerably across countries [30]. The fragmentation in reimbursement decision-making complicates the conduct of *parallel EDs*. A *parallel ED* is likely to be implementable if all stakeholders agree in advance on the selection of HTA agencies. However, given the heterogeneous preferences and interests of stakeholders, and the lack of a specific mandate, the odds of having *parallel EDs*, are relatively low.

5.1. Obligation to collect or deliver information

The different types and modes of action of MDs are numerous, and, in most cases, the manufacturer is the sole expert on the product. Hence, HTA agencies are unlikely to have the capacity to actively and continuously scan the entire complex medical device market. Furthermore, manufacturers are less likely to release business-sensitive information early. In contrast, authorities are aware of the upcoming *medicinal products*. In addition, manufacturers of *medicinal products* have more obligations related to the approval of their products and may receive various incentives, such as *orphan drug designation* or regulatory advice for *Advanced Therapy Medicinal Products (ATMP)*, for engaging the EMA early. Although the MD manufacturers have milder obligations on demonstrating evidence, the CAs and HTA agencies should define transparent processes, provide information on request, and actively com-

municate the instrument of EDs to facilitate their adoption in the context of MDs.

A *parallel ED* sounds promising, but its implementation is very complex and *regulatory* and *HTA EDs* are not fully established yet. Also, the information of the two institutions is needed at different points in time. According to our results, it is therefore advisable to first fully establish *regulatory* and *HTA EDs* and leave the consolidation of the information to the manufacturers. Once *regulatory* and *HTA EDs* have been fully established, they may be integrated into a *parallel ED*. The ED process of *EUnetHTA* [31] or the expedited pathways of the FDA [32,33], which has been tested for some time, may act as a blueprint.

5.2. The challenge of resources

The issue of resources was raised several times in our interviews. Manufacturers will make every effort to fulfill all regulatory requirements, while CAs and HTA agencies allocate few or no resources for EDs. This imbalance in resource commitment is a matter of priorities. Manufacturers have the incentive because they perceive that regulatory conformity can increase the market value of the company substantially. If more resources were to be spent on HTA before declaring conformity, then the investors would have to inject more money into the company in an early stage.

The priorities set by the CAs and HTA agencies are dictated by their statutory mandates. If the legislators do not explicitly define a mandate, these institutions do not have a legal basis to offer EDs on a large scale. A more stringent requirement for demonstrating the cost-effectiveness of MDs and a statutory mandate for the CAs and HTA agencies to offer EDs would encourage all parties to start the dialogue early. A statutory mandate is currently envisaged in the proposal for the *Regulation of Health Technology Assessment of the European Parliament and Council* [34].

5.3. Timing

The timing of an ED varies greatly according to the goal to be achieved. In *regulatory ED*, manufacturers are primarily concerned with fulfilling the *general safety and performance requirements (GSPR, Annex I of MDR)*. In *HTA ED*, the focus is on generating evidence on cost-effectiveness. Both manufacturers and authorities have indicated one year prior to market entry as a possible start of a dialogue. A dialogue on GSPRs to be demonstrated can take place earlier, and an ED about cost-effectiveness can take place later when compared to the one-year pre-market time point. However, for well-designed clinical trials that integrate clinical endpoints as well as costs for market placement and reimbursement, a simultaneous start of the ED might be beneficial. Nevertheless, an ED should be subject to the proviso that manufacturers have elaborated plans as a basis for a productive discussion.

5.4. Challenges of early dialogues in medical devices

Challenges on the side of the authorities and manufacturers include the lack of a clear legal mandate and the lack of prioritization of the HTA ED, as HTA is not a legal requirement in many countries, respectively. However, with increasing healthcare costs, more countries will introduce HTA for MDs in the future, therefore increasing the need for EDs. The specific challenges for each ED are presented in Table 2.

5.5. Limitations

The study has several limitations. First, the study could have included more respondents. However, ED is a specialist topic, and, hence, the number of qualified people is low. Furthermore, based

Table 2
Challenges of early dialogues in medical devices

	Aim	Involved parties	Timing	Challenges for authorities/agencies	Challenges for manufacturers
General				No statutory mandate	Lack of resources Obligation to inform
Regulatory early dialogue	Reduce uncertainty on which evidence must be provided for conformity assessment	CAs and NBs Manufacturer	Before defining design of clinical investigations About one or more years before DoC	Compromises auditor independence Little knowledge on new technologies	Lack of preparation/low evidence base Protection of intellectual property
HTA early dialogue	Reduce uncertainty on which evidence must be provided for reimbursement decision	HTA agencies Manufacturer	Before design of studies for HTA evidence About one year before or even after DoC	No knowledge of which emerging technologies will be introduced Faced by different types of MDs that have different evidence requirements	Numerous HTA agencies with varying assessment and appraisal criteria. Not priority for manufacturer in early development/lack of resources Lack of preparation
Parallel early dialogue	Reduce uncertainty on evidence generation Improve efficiency by combining regulatory and HTA ED	CAs (and NBs) HTA agencies Manufacturer	Several meetings starting before definition of study designs	HTA agencies are not familiar with regulatory requirements and vice versa Conflicting objectives of CAs and HTA agencies Difficulties to coordinate all stakeholders	High complexity in managing all players

CA = Competent authority; DoC = Declaration of conformity; ED = early dialogue; HTA = Health technology assessment; MD = Medical device; NB = Notified body.

on our interviews, we concluded that we had reached a sufficient level of saturation and observed a limited gain knowledge during the last interviews. Secondly, we received very few answers from the CAs, which may indicate that EDs are not a priority for them. This observation is consistent with their statutory mandate as CAs have no legal mandate for *conformity assessment*. If CAs were to play a greater role, the new MDR would have to be revised extensively. At last, our results might be biased by the interviewer, i.e., there might be a distortion related to the person questioning the informants. Although interviewer bias exists in all interviews, we believe that the effect is rather small in this study. The interviewees came from different institutions in different countries with different backgrounds. This mix attenuates potential confirmation bias or anchoring. Further, our results and conclusions went through internal review processes within our project consortium and we believe that severe biases would have been identified by our experts.

6. Conclusion

EDs might have the potential to expedite access to innovative and potentially life-saving MDs. For a successful implementation of *parallel EDs*, *regulatory* and *HTA EDs* should be fully established. This effort requires the initiative of the manufacturers to engage the CAs and HTA agencies early. Furthermore, the legislator plays an important role, as the legislator can create the legal basis and set the right incentives for manufacturers to initiate change.

Declaration of Competing Interest

The authors declare that they have no financial/personal interest or belief that could affect their objectivity other than the stated funding source.

Author agreement

All authors have seen and approved the final version of the manuscript. The authors warrant that the article is the authors' original work, hasn't received prior publication and isn't under consideration for publication elsewhere.

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Supplementary materials

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