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Challenges with coverage with evidence development schemes for medical devices: A systematic review

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ABSTRACT

Objectives: Coverage with evidence development (CED) schemes are particularly relevant for medical devices (MDs), since clinical evidence is often limited at the time of launch and their long-term (cost-) effectiveness heavily depends on how they are adopted into routine clinical practice. The objective of this study was to identify and describe the challenges that payers and manufacturers might face when assessing the desirability of, choosing the research design for, implementing, and evaluating CED schemes for MDs.

Methods: A systematic literature review was performed on six databases following PRISMA guidelines. Two independent reviewers assessed the eligibility of studies based on predefined criteria and extracted data from the included articles by using a pre-defined extraction template. The data were synthesised in a narrative review.

Results: The systematic search yielded 4293 articles of which 27 were eligible for inclusion. We identified 20 challenges that are associated with CED schemes for MDs. Five of these challenges relate directly to the characteristics of MDs, and hence are specific to MDs. These challenges concern deciding on whether a CED scheme is required, understanding the relevant uncertainties and risks, identifying meaningful outcomes, defining an adequate duration for a scheme, and market entry of new technologies.

Conclusions: Payers and manufacturers of MDs have to address the identified challenges to improve a CED scheme's chance of success. This can be further improved by public sharing of information about the outcome of applied schemes and way in which stakeholders have addressed the challenges they faced when applying a CED scheme.

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Introduction

Decisions about the coverage and reimbursement of new health technologies are inherently uncertain as, at the time of market launch, only limited information is available about their real-world performance [1]. Uncertainties typically concern: (1) the safety and (relative) clinical effectiveness of a technology in a specified patient population, measured by short- and long-term outcomes that are relevant for patients, (2) the value for money of a technology and the question whether its reimbursement is considered an efficient use of available resources, (3) the adoption and diffusion of a technology, such as the rate of uptake, disease areas in which the technology may be used, possible off-label use, and number of patients who may benefit from the technology, and, related to this, (4) the budget impact following adoption, i.e. the financial impact on the healthcare system, including additional costs and cost savings associated with reimbursing the technology [e.g. 1–4].

These uncertainties may be considerable, especially when coverage and reimbursement decisions are taken close to the time of product approval (e.g. licensing or Conformité Européenne

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marking) and when they are inextricably linked to the characteristics of the technology, as is often the case for medical devices (MDs) [1]. For example, MDs frequently undergo product modifications that may affect their efficacy and costs, they often have multiple applications, and their efficacy may not only depend on characteristics of the MD itself but also on the skills and experience of those applying a MD in clinical practice [5]. Furthermore, uncertainties associated with safety, efficacy, and (cost-) effectiveness may be particularly relevant for MDs, as requirements for product approval are often less clear and the level of evidence supporting regulatory and market approval are typically less stringent than for pharmaceuticals [5–7]. Although market approval regulations for MDs will become more stringent in Europe from May 2020 onwards, the uncertainties associated with coverage and reimbursement of MDs will likely continue to exist as the most stringent rules will only apply to a small number of MDs, i.e. class III (high-risk) MDs, including implants [7,8], and even these rules do not eliminate the full range and extent of uncertainty highlighted above.

Traditionally, payers have borne the financial risk of making 'wrong' coverage and reimbursement decisions in the presence of uncertainties regarding the real-world performance of health technologies. A wrong decision may occur when a health technology is reimbursed for which later its original claims on safety, efficacy, and/or (cost-) effectiveness are not confirmed (type I error) or when a technology is not reimbursed but later is shown to be more safe and (cost-) effective than relevant comparators used in clinical practice (type II error) [6,9,10]. Regardless of the type of error, any wrong decision is undesirable as it will likely always lead to loss of benefits to patients (directly or indirectly) and an inefficient use of available resources. The risk of making a wrong decision and the evidence gap between requirements for regulatory and market approval on the one hand and coverage and reimbursement decisions on the other hand have led to the introduction and increased use of 'coverage with evidence development (CED)' schemes [e.g. 2,4,10].

CED schemes aim to reduce uncertainties associated with the safety, efficacy, and (cost-) effectiveness of health technologies. They allow temporary reimbursement of the MD, while more data are being collected to enable making a better informed decision at a later stage, while sharing the risk of a wrong positive (temporary) coverage or reimbursement decision between payers and manufacturers during a CED scheme [e.g. 1,3,6]. Thus, they avoid uncertain and potentially wrong negative decisions and allow more informed decisions without delaying access to the MD for patients. These schemes go under different names in different countries, for example, 'coverage with evidence development schemes' in the USA, 'conditionally funded field evaluations' in Canada (Ontario), 'interim funding schemes' in Australia, 'only in research (OIR)' and 'only with research (OWR)' in the UK (England/Wales), and 'conditional reimbursement schemes' in Belgium and the Netherlands [12,14]. However, these schemes can all be labelled as performance-based risk sharing agreements (PBRSAs), i.e. "a plan by which the [clinical] performance of the product is tracked in a defined patient population over a specified period of time and the level or continuation of reimbursement is based on the health and economic outcomes achieved" [1]. Following this definition, CED schemes cover schemes that manage utilization in the real world and link reimbursement to the performance of a health technology as well as schemes that provide additional evidence with the aim to reduce decision uncertainty [1].

Despite the growing interest in CED schemes, they are often costly, complex, and challenging [2,15]. In response to these challenges, ISPOR's 'Good Practices for PBRSA Task Force' formulated four *good practice questions* that need to be addressed when considering the use of a CED scheme. These questions concern: (1) the desirability of the scheme (as opposed to some other reimbursement or research arrangement), (2) the choice of research design, (3) the approach to implementation, and 4) the method used for evaluating the scheme [1]. In principle, the use of CED schemes seems particularly relevant to MDs, since clinical evidence is often limited at the time of launch and the long-term effectiveness and cost-effectiveness is heavily dependent on how they are adopted into routine clinical practice. Therefore, the objective of this study was to identify and describe the challenges that payers and manufacturers might face in light of the four good practice questions when applying CED schemes for MDs. The results should be of interest to those who (consider to) apply or design CED schemes for MDs and want to improve a scheme's chance of success.

Methods

The systematic review was conducted following the Preferred Reported Items for Systematic Review and Meta-Analysis (PRISMA) framework [16]. The PRISMA checklist is available as Supplementary Material S1.

Eligibility criteria

We included studies in the review if they met the following eligibility criteria: (1) the article is a primary study, meta-analysis/review, letter, editorial, or note, (2) the article discusses (in-depth) the challenges associated with CED schemes for MDs, (3) the article is written in English, Italian, Spanish, Portuguese, or Dutch, (4) the article is published between 2000 and 2019, and (5) the full text is available.

Following the European Union Directive 2007/47/EC, we defined MDs as "any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, together with any accessories, 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, treatment, monitoring or alleviation of disease". For our main analysis, we included studies that discussed challenges with CED schemes (i) in the specific context of MDs and (ii) the context of different types of health technologies if this included MDs. To enable a secondary analysis, in which we compared challenges associated with CED schemes for MDs with those for pharmaceuticals, we also included studies that discussed challenges with CED schemes solely in the context of pharmaceuticals. We excluded studies that merely reported on the characteristics, processes, and/or results of applied CED schemes for MDs and that discussed challenges solely in the context of financial agreements between payer and manufacturer, e.g. price volume agreements, budget capping, and discounts.

Data sources and search strategy

To identify studies that discussed challenges associated with CED schemes for MDs, we conducted a search on the Web of Science (WoS), Pubmed (National Library of Medicine), Embase, and Scopus databases in September 2018. We supplemented this with a search on the Google and Google Scholar databases in the same month and updated this search in January 2019. Furthermore, we performed a check on the reference lists of all full texts that we reviewed for eligibility for relevant studies that did not show up in our search results. The full electronic search strategy used for WoS is available as Supplementary Material S2. This search strategy was adapted for use on the other bibliographic and Google databases. We did not register a systematic review protocol.

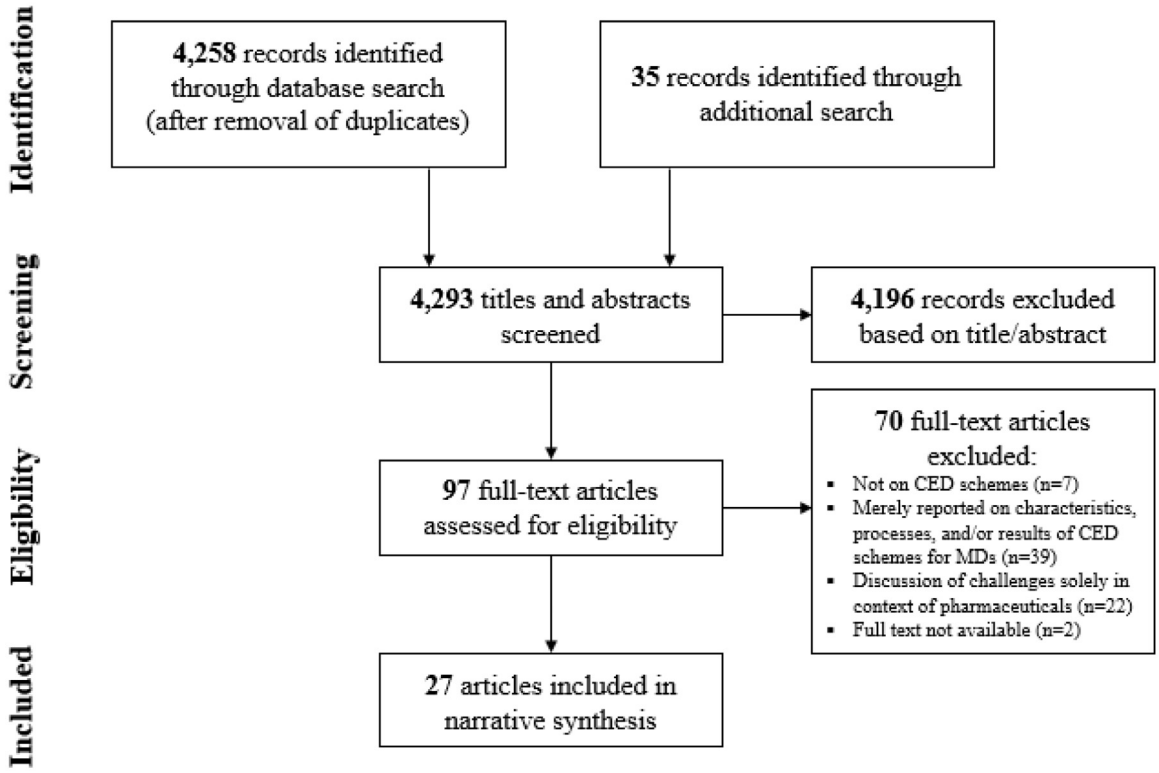

Fig. 1. PRISMA flowchart of selection process

Study selection

Two reviewers (VRD and CF) independently screened the titles and abstracts of all articles based on the predefined eligibility criteria. Subsequent to the screening of titles and abstracts, the reviewers compared results and resolved disagreements by means of dialogue. Articles that were potentially eligible for inclusion and those for which the dialogue could not settle disagreement between the reviewers were selected for full-text review. The reviewers then independently reviewed the full texts, compared results, and again resolved disagreement by dialogue. Articles were included in the review if they met all eligibility criteria and both reviewers agreed on their inclusion.

Data abstraction

The same two researchers applied a directed context analysis approach to extract data from the selected studies [17], by using a pre-defined extraction template in Microsoft Office Excel. The following data were extracted: (1) author(s), (2) year, (3) country, (4) type of study, (5) type of health technology, (6) CED scheme for MD and the associated medical condition, (7) challenges associated with assessing the desirability of a CED scheme, (8) challenges associated with choosing the research design for a CED scheme, (9) challenges associated with the implementation of a CED scheme, (10) challenges associated with the evaluation of a CED scheme, and (11) 'other' types of challenges associated with a CED scheme for MDs, where items 7–10 relate to challenges associated with the four *good practice questions* described in the Introduction section and item 11 relates to challenges that fall outside the scope of these questions [1]. The data were synthesised in a narrative review [18].

Although we excluded studies that discussed challenges with CED schemes for pharmaceuticals from our main analysis, we also extracted the data from these studies in order to examine the similarities and differences between challenges associated with CED schemes for MDs and pharmaceuticals.

Results

Search results

The database search yielded a total of 4293 unique records; 4258 records were yielded from WoS, Pubmed, Embase, and Scopus, and 35 from Google and Google Scholar. The screening of titles and abstracts resulted in the exclusion of 4196 records. The full-text review resulted in the exclusion of another 70 records. The main reasons for exclusion were merely reporting on the characteristics, processes, and/or results of applied CED schemes for MDs (n = 39) and discussion of challenges solely in the context of pharmaceuticals (n = 22). The remaining 27 articles met all eligibility criteria and were included in the review. Fig. 1 presents the PRISMA flowchart of the selection process.

Study characteristics

Table 1 presents an overview of the general characteristics of the included articles. Of the 27 studies included in the review, 6 reported on challenges with CED schemes in the specific context of MDs and 21 on challenges with CED schemes in the context of different types of health technologies, including MDs. Most studies focused on one or more CED schemes applied in the USA (n = 10), followed by one or more European countries (n = 9), Australia (n = 6), and Canada (n = 6). A total of 16 studies discussed the challenges in the context of 55 existing CED schemes for MDs. Most of these schemes were applied in Canada (Ontario) (n = 13), followed by the USA (n = 11), UK (n = 9), Australia (n = 5), the Netherlands (n = 5), Germany (n = 5), France (n = 3), Belgium (n = 3), and Spain (n = 1).

Table 1
General characteristics of the included articles

#	Author(s) [ref]	Year	Country of focus	Type of Study	Type of health technology[a]	CED scheme(s) for MDs and associated medical condition[b]
1	Tunis and Pearson [25]	2006	USA	Theoretical	All technologies	ICDs for the prevention of sudden cardiac death in high-risk patients, Balloon angioplasty plus carotid stenting for patients with carotid artery disease, FDG-PET scan for diagnosis of dementia and various cancer types
2	Hutton et al. [26]	2007	NS	Theoretical	All technologies	NS
3	Lindsay et al. [27]	2007	USA	Case study	MDs	ICDs for the prevention of sudden cardiac death in high-risk patients, FDG-PET scan for various cancer types
4	Carbonneil et al. [14]	2009	Australia, Belgium, Canada (Ontario), UK (England/Wales), Germany, Spain, USA	Systematic review; Survey; Interviews	All technologies	Belgium: DBS, Endovascular treatment of abdonimal aneurysms, DES for diabetic patients, Cochlear implants; Canada (Ontario): PET scan, DES, cardiac CT angiography; France[c]: intensity-modulated radiation therapy, extracranial stereotactic radiotherapy; TAVI; Germany: screening for skin cancer; Spain: PET scan; USA: Cochlear implants, ICDs, PET scan
5	Dhalla et al. [28]	2009	UK	Survey	All technologies	HealOzone for treatment of tooth decay, Endovascular stent insertion for intracranial atherosclerotic disease, Soft-palate implant for simple snoring
6	O'Malley et al. [6]	2009	Australia	Case study	MDs	PillCam® Capsule Endoscopy for the evaluation of obscure gastrointestinal bleeding
7	Goeree et al. [29]	2010	Canada (Ontario)	Case study; Theoretical	MDs and surgical procedures	DES for patients with different medical conditions
8	Menon et al. [30]	2010	Australia, Canada (British Columbia, Ontario, and Alberta), UK, USA	Consensus statement	All technologies	NS
9	Mohr and Tunis [24]	2010	USA	Case studies	All technologies	Carotid artery stenting, Haemodialysis, FDG-PET for diagnosis of dementia and various cancer types, ICDs, Cochlear implant, Long-term oxygen therapy, Artificial heart, Sleep Apnoea, SCS for patients with chronic back and leg pain, Magnetic resonance guided focused ultrasound for the treatment of uterine fibroids (pilot)
10	Stafinski et al. [2]	2010	NS	Review	All technologies	Australia: EVAR for treatment of abdominal aortic aneurysm, DBS for patients with Parkinson's disease no longer responsive to pharmaceutical therapy, PET scan for various cancer types; Canada (Ontario): EVAR for treatment of abdominal aortic aneurysm, DES for patients with coronary artery disease, PET scan for various cancer types, diagnosis of solitary pulmonary nodule diagnosis, and patients with left ventricular dysfunction for whom revascularisation or cardiac transplantation was considered, EP for patients with refractory cutaneous T-cell lymphoma, MDCTA for diagnosis of coronary artery disease, ICDs for prevention of sudden cardiac death in patients with coronary heart disease, PVP for patients with benign prostatic hyperplasia, HBOT for treatment of chronic, non-healing, ulcers of the lower limb for patients with diabetes mellitus, NWPT (VAC system) for patients with chronic pressure wounds of the pelvic region; The Netherlands: SCS for patients with chronic non-oncological pain; USA; carotid artery angioplasty and stenting for the prevention of stroke in patients with carotid artery disease; PET scan for diagnosis of dementia and various cancer types, ICDs for prevention of sudden cardiac death in patients with life-threatening cardiac dysfunction, Long-term (home) oxygen treatment for patients with COPD, Artificial hearts for patients with severe biventricular end-stage heart disease who are not transplant candidates
11	Trueman et al. [31]	2010	NS	Summary of conference presentations; Review	All technologies	Canada (Ontario): DES
12	Levin et al. [32]	2011	Canada (Ontario)	Case studies	All technologies	DES, EVAR, 64-slide CT angiography, PET scan for various cancer types, EP, Insulin infusion pumps in the management of insulin-dependent type 2 diabetes
13	Mortimer et al. [33]	2011	Australia, UK, USA	Theoretical	All technologies	Australia: DBS for patients in Parkinson's disease, TUNA

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Table 1 (*continued*)

#	Author(s) [ref]	Year	Country of focus	Type of Study	Type of health technology[a]	CED scheme(s) for MDs and associated medical condition[b]
14	Relyea-Chew [34]	2011	USA	Case studies	All technologies	PET scan for diagnosis of dementia/neurodegenerative diseases and various cancer types
15	Claxton et al. [22]	2012	NS; UK (England/Wales)	Review; Case studies	All technologies	Canada: PET scan; USA: ICD, PET scan; UK (England/Wales)[d]: Prostheses for primary total hip replacement, Hearing aid technology, Metal on metal hip resurfacing for patients with hip disease, Photodynamic therapy for (age-related) macular degeneration, Carmustine implants for patients with glioma, SCS for patients with (chronic neuropathic or ischaemic) pain, Cochlear implants for patients with hearing impairment, Endovascular stent-grafts for patients with abdominal aortic aneurysm
16	Walker et al. [35]	2012	NS	Theoretical	All technologies	NS
17	Bishop and Lexchin [36]	2013	Australia, Canada, UK, USA	Interviews	All technologies	NS
18	Garrison et al. [1]	2013	NS	Case studies; Theoretical; Taxonomy	All technologies	USA: PET scan for various cancer types, Percutaneous transluminal angioplasty and stenting for prevention of a second stroke, SCS for failed back surgery syndrome
19	Brügger [12]	2014	Australia, Belgium, Canada (Ontario), France, Germany, The Netherlands, Sweden, Switzerland, USA	Review; Case studies; Interviews	All technologies	Australia: HBOT for patients with non-diabetic ulcers; Canada (Ontario): DES, PET scan; Germany: PET scan for colorectal cancer, Balneo-phototherapy for patients with psoriasis, VAC therapy for chronic wounds, Brachytherapy for patients with prostate cancer; The Netherlands: Radiofrequency denervation for patients with chronic non-specific low back pain, Intra-arterial thrombolysis/thrombectomy in a stroke unit, Renal denervation for patients with treatment-resistant hypertension, Transluminal endoscopic step-up approach in patients with infected pancreatic necrosis; USA: PET scan, Artificial hearts, TAVI, Cochlear implant, FDG-PET scan for diagnosis of dementia
20	Foster et al. [37]	2014	USA	Commentary	MDs	FDG-PET scan for patients with dementia
21	Launois et al. [38]	2014	NS	Theoretical; Taxonomy	All technologies	NS
22	Martelli and van den Brink [39]	2014	France	Theoretical	MDs	NS
23	Drummond [13]	2015	NS	Theoretical	All technologies	NS
24	Garrison et al. [40]	2015	USA	Review; Survey; Interviews	All technologies	NS
25	Kanavos et al. [23]	2017	NS	Theoretical; Taxonomy	All technologies	NS
26	Rothery et al. [19]	2017	NS	Theoretical	MDs	NS
27	van de Wetering et al. [15]	2017	The Netherlands	DCE	All technologies	NS

COPD, chronic obstructive pulmonary disease; CT, computerised tomography; DBS, deep brain stimulation; DCE, discrete choice experiment; DES, drug-eluding stents; EECP, enhanced external counterpulsation; EP, extracorporeal photopheresis; EU, Europe; EVAR, endovascular aneurysm repair; FDG-PET, fluorodeoxyglucose - positron emission tomography; HBOT, hyperbaric oxygen therapy; HTA, health technology assessment; ICD, implantable cardioverter-defibrillator; MD, medical device; MDCTA, multidetector computed tomographic angiography; NICE, National Institute for Health and Care Excellence; NPWT, negative pressure wound therapy; NS, Not Specified; PET, positron emission tomography; PVP, photo selective vaporisation of the prostate; SCS, spinal cord stimulation; TAVI, transcatheter aortic valve implantation; TUNA, transurethral needle ablation; UK, United Kingdom; USA, United States of America; VAC, vacuum-assisted closure system

[a] All technologies are including MDs.

[b] The associated medical condition is presented if specified by the authors.

[c] Recommended by national HTA agency, but scheme not initiated.

[d] Recommended by NICE.

Challenges associated with CED schemes for MDs

We extracted information on 17 challenges from the included studies that were associated with assessing the desirability, choosing the research design, implementation, evaluation, and 'other' types of challenges with CED schemes for MDs. In particular, these 17 challenges concern: (1) deciding on whether a CED scheme is desirable, (2) understanding the relevant uncertainties and risks, (3) lengthy and complex negotiations, (4) defining the decision problem, (5) data requirements, (6) identifying meaningful outcomes, (7) defining an adequate duration for a scheme, (8) market entry of new technologies during a scheme, (9) obtaining funding, (10) obtaining informed consent, (11) quality of the data, (12) deciding on when a scheme is considered successful, (13) withdrawing a technology, (14) lack of transparency, (15) lack of governance, (16) stakeholder involvement, and (17) ethical issues. Table 2 presents a description of each of these challenges. A full overview of the extracted challenges, including those extracted from studies discussing the challenges solely in the context of CED schemes for pharmaceuticals, is available as Supplementary Material S3.

These challenges apply to some extent to all CED schemes for different types of technologies; however, five relate directly to the characteristics of MDs, and hence are specific to MDs. Most of these specific challenges were discussed by Rothery et al. (2017) and relate to deciding on whether a CED scheme is required,

Table 2
Challenges associated with CED schemes for MDs[a]

	#	Challenge	Description
Desirability	1	Deciding on whether a CED scheme is required	Whether CED schemes are recommended depends on both the characteristics of the technology (whether it is expected to have a positive net benefit, whether evidence can be generated following reimbursement, and whether there would be a cost in reversing the decision at a later data) and the range of authority of the purchaser (whether they can delay a decision or review it at later date, whether they can negotiate price, and whether they can ensure that research is actually conducted) [35]; Generally, there is a lack of criteria and formal guidelines that can help decide whether a CED scheme can help reduce uncertainty and should be initiated [12,28,39]; The question of whether or not further research is worthwhile requires some assessment of how uncertain a decision based on expected cost-effectiveness might be, what the consequences are likely to be if an incorrect decision is made, and what a technology that has been subjected to a CED scheme is displacing [22]; There is a close link between the value of a MD, the value of further research to reduce uncertainty and the price of the MD. These links can offer incentives for manufacturers to price accordingly and decide whether there is sufficient value from further evaluative research. The value of additional research can be informed through VOI analysis [19]. However, VOI analysis may be difficult to apply in specific cases and a formal guideline may help decide whether research in a particular area is practical and likely to reduce uncertainty [28]. This should be enhanced, in particular by clearly stating the selection criteria for MDs that may benefit from such approaches [39]; There is a concern that CED schemes could stifle or slow innovation by creating a disincentive to develop new products for conditions for which the evidence base is not well developed or by raising the evidentiary standards [24,41]; CED schemes may have the unintended effect of lowering industry investment in evidence development and shifting research costs to public fund holders [33]; There is a concern that manufacturers use CED schemes as a mechanism to secure beneficial formulary placement, gain market share, and increase patient compliance. Manufacturers may be reluctant to take on the risk of a CED scheme when they cannot predict how their product will be used in the real-world population [40].
	2	Understanding the relevant uncertainties and risks	There are challenges in assessing risks upfront due to uncertainties in the real-world performance of a technology and further research is unlikely to be able to resolve all uncertainty [31,33]; Some uncertainties cannot be reduced by further research and may resolve by other changes occurring over time. For example, the effective price of the technology and/or its comparators may change. The price plays a key role in determining the value of the technology, but it also affects the level of uncertainty by changing the likelihood of making an incorrect decision and the value of further research [19]. Other uncertainties that cannot easily be resolved by further research may concern previously unrecognised adverse effects that emerge in the long term and changes in market conditions that might cause the price of the technology to drop in the future [13]; One of the complexities associated with the evaluation of MDs is the fact that any decision about the adoption of the MD will interact with the ability to gather more evidence and may affect future commercial developments of the technology [19]; There is a group of concerns relating to the introduction of additional uncertainty for manufacturers in terms of expected returns, which may have the opposite effect of dis-incentivising additional data collection, the advantage competitors may take of data collected by the manufacturer, and related to this is the problem of free-riding [23].
	3	Lengthy and complex negotiations	Defining the study design is often lengthy and complex, and it may be difficult to reach contractual agreement [32,40]; Deciding on the point in the product life cycle at which a technology should be assessed is a contentious issue and various stakeholders may have different views on the technologies that require further study, the questions that need to be answered, and the necessary methods for answering those questions. It requires the creation of working groups made up of key stakeholders and opinion leaders who are involved in designing the study questions and methods from the beginning of the process [25,26]; There is protocol development, sample size and site determination, case report form development, contracts with sites and investigators and dealing with multiple ethics boards submissions, therefore, study initiation is often subject to contractual and legal delays [32].
Research design	4	Defining the decision problem	The decision problem is rarely stated explicitly and this creates the risk that the study design does not address the decision problem or is not designed to feasibly address that problem [30]; The research design that is most appropriate depends on the nature and type of the uncertainty that the CED scheme is trying to address, e.g. uncertainty about whether the medical product or service will be used in the right patients or uncertainty at launch about clinical or economic outcomes [42].
	5	Data requirements	A formal guideline for CED schemes should be accompanied by a clear statement regarding what study design and data are required to reduce uncertainty [45]. Requirements are often not specified and laws can be unclear at this point [39]; The study design that is required to answer questions of evidence development is often not clearly defined, especially concerning the need for RCTs or observational/not experimental designs [31]; For the establishment of registries, there are generally no guidelines available [6]; The design of a study should not take place when the decision is made over who should pay for the study as this may impose restrictions [22].
	6	Identifying meaningful outcomes	Outcome measures should be clear, measurable, objective, realistically achievable (in relation to the duration of the scheme), and relevant [1]; It is important to be certain that the outcomes of interest are largely influenced by the technology concerned [13]; Manufacturers and payers may shy away from agreements in disease areas where there are many different treatment paradigms or the relevant outcome is an intermediary outcome, because it can be challenging to attribute the outcome to the product in question. There is also a risk for manufacturers with being responsible for outcomes when they cannot control the way a technology is used [40]; Uncertainty about the efficacy of a MD and the learning or training required to achieve the desired efficacy can result in adverse consequences on patient outcomes and lead to an ineffective use of healthcare resources [19]; When questionnaires for data collection are designed by physicians, they may not be ideal for use in an economic analysis [6]; In some cases, the 'right' outcomes may not identified until the scheme is implemented, resulting in failure to capture the data needed to reduce the decision-making uncertainty [2].

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Table 2 (*continued*)

	#	Challenge	Description
	7	Defining an adequate duration for a scheme	Designing the necessary clinical research, getting funding, and implementing a scheme in a time frame that is consistent with the needs of clinicians, patients, and other decision makers is challenging [25]; With a typical three- to five-year political cycle, there is often a tension between research and political needs [29]; Short-term schemes are not desirable given the considerable investment in evidence development, while long-term deals are also not desirable given the costs and risks involved [40]; The unique characteristics associated with MDs, such as rapid incremental innovation, learning effects, and upfront irrecoverable costs all present a challenge for the timing of reimbursement decisions and the value of waiting until additional evidence is conducted to support the technology [19]; In view of the pace of technological changes in healthcare, a CED scheme of more than three years may be of limited relevance for MDs [26,43]. This is because the kinds of policy questions that such studies inform have the habit of changing, for example, as other technologies become available for the same patient group [13].
	8	Market entry of new technologies	The information generated by research will not be valuable indefinitely as new and more effective interventions may become available and make the information no longer relevant for future clinical practice [19]; Market access of incremental MD innovations and new technologies may make existing ones obsolete or change their cost-effectiveness [26,33]; Rapid approval of new entrants may result in a disincentive for manufacturers to invest in further research that would reduce uncertainties about MDs efficacy [19]; MDs that enter the market during a CED scheme may not be included in the scheme, and hence reports may be based on evidence from only one MD [6].
Implementation	9	Obtaining funding	The costs associated with CED schemes can be substantial and a barrier to establishing a viable and cost-effective scheme [1,28,29,36,40,44]; CED schemes are perceived to have high transaction costs and be difficult to execute, particularly given the fragmented payer system with patient movement across plans, as well as the current lack of data infrastructure that limits feasibility and, to some extent, interest in measuring long-term outcomes [40]; It may take years before funding is ensured and then there may still not be sufficient funding to generate the evidence needed to reduce uncertainties and meet the HTA agency and decision makers requirements [14,22,25]; Lack of experience with CED schemes, staff turnover, billing requirement complexity, and inconsistency of nonresearch and research requirements may add up to significantly more time and effort than anticipated, at times for studies with no funding for administration [37]; Some have suggested establishing public-private partnerships between payers and manufacturers, while others have stressed the importance of locating publicly funded research organizations who may be perceived as neutral and, therefore, better able to provide control over research design and data, and manage vested interests [2,31].
	10	Obtaining informed consent	Identifying and counselling potential participants and obtaining informed consent requires considerable effort and patients may decline to participate or may prematurely withdraw. The need for frequent reconsent, e.g. when regulations change mid study, should be taken into account [37]; If patients or physicians withhold consent, the patients' data will not be used for research, but it will still be stored, e.g. in a registry, and may still be reimbursed under a CED scheme [27].
Evaluation	11	Quality of the data	It may be difficult to obtain consensus amongst stakeholders about what is considered an acceptable quality of evidence [22]; After coverage or reimbursement is obtained for a technology, there may be a lack of incentive, e.g. for manufacturers, to collect the data [25]; There is the risk that research may not happen, does not answer the initial questions, does not feed back into decision making and the technology is funded anyway, or does not deliver the evidence while the funding cannot be stopped [12]; Evidence generated may not meet the quality criteria or be sufficient for making coverage decisions, e.g. when relying on observational data alone [2,12,14]; The accuracy, reliability, and completeness of the data, e.g. when submitted to a registry, often depends on physicians and they may not always have the necessary time to complete the forms accurately [5,17,28]; Physicians are not (always) paid for data collection and reporting, which may affect the quality of the data, and there may substantial missing data, e.g. due to loss to follow-up in registries, which may lead to bias [6]; There is an additional burden to monitoring a CED scheme and of collecting and analysing the data collected as part of a CED scheme. This may affect the quality of the data [26]; For the success of a scheme, it is imperative that payers and manufacturers trust the data and clear agreements on data validation and analysis are important to create this trust [40].
	12	Deciding on when a CED is considered successful	There still is little evidence to support the claimed benefits of CED schemes and the extent to which some of the challenges involved in CED scheme implementation impact on the final outcome [23]; It is not clear if CED schemes succeed in limiting reimbursement to specific patient subgroups and payers are sceptical that CED schemes will reduce costs in the long run [23,24]; As it may not be possible to assess the VOI generated by a CED scheme directly post hoc, there is a need to rely on process indicators for assessing a scheme's success. Such process indicators should relate to the research questions relating to the design, implementation and evaluation of the scheme and include the questions, i.e. are the intended outcome measures collected, was uncertainty in associated parameter estimation reduced for the outcomes that were the focus of the scheme, did the scheme run to budget and time, was the integrity of the design/estimation maintained, did the governance arrangements work well, and did the success to underpin a decision with further evidence prove successful [1]; Whether the CED scheme has achieved its objectives and can be considered good value from a health system perspective is linked to the desirability of the scheme and can be addressed from multiple perspectives: manufacturer, patient, payer, provider, and society. A comprehensive evaluation will therefore need to consider multiple perspectives [1]; The success of CED schemes when manufacturers are asked to conduct the research will depend on whether the authorities are able to establish contractual arrangements as part of a CED scheme, that is, arrangements that can be monitored and enforced with credible penalties to ensure that agreed research is conducted and in the way intended [22].

(*continued on next page*)

Table 2 (*continued*)

	#	Challenge	Description
	13	Withdrawing a technology	Once a technology is used in practice–even if formally temporary–ending reimbursement may be less feasible than initially not reimbursing it, especially when the technology proves to be effective, but not cost-effective [1,15,26]; Decisions to withdraw may cause heated discussions with doctors, patients, and politicians and be followed by a public debate in the media [12]; Patients may also be more motivated to exert political pressure to secure or maintain coverage of last-line treatment for life-threatening illnesses than for preventative or 'me-too' interventions. Inertia in clinical practice may be a barrier to delisting, particularly for interventions with a long-standing place in both formularies and clinical practice. Payers may adopt a passive role and rely upon clinicians to modify their prescribing practice to replace inferior interventions with more effective or better-tolerated alternatives as and when they become available. Evidence development may be delayed if the default position is to extend funding until the data become available [33].
Other	14	Lack of transparency	There is a general lack of information on CED schemes in the public domain that is attributed to 'commercial confidentiality'. Consequently, payers who consider CED schemes as a potential policy option have little information upon which to base a decision [2]; There is little information available on the agreements implemented, their objectives, and evaluation of their impact. This prevents cross-country learning and limits the ability of patients to engage with CED processes [23]; Disclosure of the results of previous schemes related to a technology of interest may reduce duplication of efforts. Mechanisms for increasing transparency around key components, e.g. objectives, conflicts of interest, data collection management, and oversight, of the scheme that respect commercial interests are required to build on previous good research practices for specific types of studies [1,2].
	15	Lack of governance	Lack of project management and coordination can be an obstacle for CED schemes and can make it difficult to ensure an update of the recommendation following the production of new evidence [12,14,22]; The independence of a scheme from any party with a vested interest in its outcomes should be ensured [30]; Stakeholders may take contradictory positions (also amongst themselves) around where the leadership should rest and which stakeholders should be involved in a CED scheme [36]; Supervision of the research may create a conflict of interest for a HTA body as they need to keep the image of being a helper for a better quality healthcare system [12].
	16	Stakeholder involvement	The various stakeholders can affect political decisions around the initiation of a CED scheme. For example, manufacturers may pressure the initiation of a scheme and conflicts of interest may arise when manufacturers play a role in the funding, data collection, and evaluation of a scheme [36]; Patients, generally, have limited opportunities to engage in the development of a scheme and not all patient groups are aware of what CED schemes entail [23]; Patient advocacy groups may be unwilling to accept this policy especially if the assessed treatment is considered to be safe and efficacious [22]. They may distrust the motives of payers in their efforts to support evidence development through coverage, and may assume that the primary objective is cost containment, rather than a genuine effort to support early access to innovations and clinical research [24]; There may be significant opposition from the clinical community and compliance with data collection by physicians may be weak, e.g. because of lack of staff [11,31]; There is the risk that CED schemes are perceived as a tool for monitoring or controlling physicians, particularly in the context of registers on interventional procedures with or without the use of MDs [40]; Compliance with data collection by physicians may be weak and the monitoring of the study poor because of lack of clinical staff [12]; The translation of evidence into policy is riddled with political and economic considerations, both the overt political process involved in CED and the role of the pharmaceutical industry. The most explicit evidence of relations of power comes from the hierarchy of roles in the decision-making process. Political influences play a role in determining where the money for CED will come from and where the ultimate decision-making comes from [36].
	17	Ethical issues	CED schemes may be beneficial for future patients, but they can impose significant opportunity costs on current patients. Some individuals in the present population may benefit from the research condition because they will also be members of the future population. However, this will not be true for all and so the issue of balancing the interests of some individuals in the present population against some individuals in the future population remains [22]; Various stakeholders, e.g. policy makers and patient groups, have questioned whether it is ethical to restrict access to technologies to patients participating in registries and clinical trials, and to withhold a potentially beneficial innovation from a subset of patients who cannot, or will not, participate while providing it to another [12,22,24,25,31,34]. It is also questioned whether study participation concerns coercion and whether patients' informed consent is valid in this context [24,25,34]; Patient advocacy groups may be unwilling to accept a CED scheme, especially if the treatment has demonstrated safety and efficacy [31]; Furthermore, CED schemes may result in inequities as participants in the treatment arm may receive better treatment than those in the other arm and those not participating, and treatments may not be available in all geographical areas [22,34].

AWR, approval with research; CE, Conformité Européenne; CED, coverage with evidence development; FDA, Food and Drug Administration; GRP, good research practice; NICE, National Institute for Health and Care Excellence; OIR, only in research; RCT, randomised controlled trial; USA, United States of America; VOI, value of information.

[a] For reasons of clarity, we used the term CED scheme in this table, where the author(s) at times used the terms performance-based risk sharing agreement or access with evidence development scheme. The original terms used by the author(s) can be found in Supplementary Material S3. The classification of challenges into 'Desirability', 'Research design', 'Implementation', and 'Evaluation' of CED schemes relate to the four *good practices questions* that were formulated by ISPOR's 'Good Practices for PBRSA Task Force' [1]. 'Other' relates to challenges that fall outside the scope of these questions.

understanding the relevant uncertainties and risks, identifying meaningful outcomes, defining an adequate duration for a scheme, and market entry of new technologies. For example, it may be particularly challenging to decide whether a CED scheme is required for a MD as the prices of MDs are likely to change over time due to rapid incremental MD innovations and market entry of new MDs. This may directly impact the uncertainty associated with making a wrong coverage or reimbursement decision and the value of further research into MDs' cost-effectiveness. Incremental innovations, high upfront irrecoverable costs, and market entry of new MDs may also result in a disincentive for (individual) manufacturers to invest in research that would reduce uncertainty about MDs'

efficacy. This may lead to a situation in which research costs shift to public fund holders. Furthermore, the changes over time in prices of MDs and due to gradual innovations can complicate defining an adequate duration for a scheme and this, in turn, may impact the identification of and data collection on meaningful outcomes. The identification of meaningful outcomes may also be particularly challenging for MDs as the outcomes of interest are typically not only influenced by the MD, but also by the subsequent treatment, e.g. as is the case for diagnostic MDs such as positron emission tomography (PET) scans. Furthermore, MDs' effectiveness is not only influenced by characteristics of the MD itself but may to a large extent be influenced by the learning or training of physicians that is required to achieve the optimal effect. The associated learning curve of physicians may result in a more modest impact on patient outcomes or higher costs during the early use of MDs, resulting in a lower cost-effectiveness of MDs when assessed in the short run or early in the development phase.

A qualitative assessment of the similarities and differences between challenges associated with CED schemes for MDs and other types of technologies, e.g. pharmaceuticals, did not reveal any challenges with CED schemes for other types of technologies that do not also apply to MDs. However, we identified three challenges that were discussed in the context of CED schemes for pharmaceuticals that were not found in the included studies, yet are also considered to be applicable to MDs. The first challenge concerns the information asymmetry between payers and manufacturers about the potential real-world performance of a technology and the impact this may have on CED-scheme agreements [20]. The second challenge concerns the ex-ante definition of a final decision rule based on the gathered information and 'exit strategy'. It needs to be defined when the (cost-) effectiveness and/or safety of a technology is deemed to be below expectations or some relevant threshold, leading to its withdrawal or a premature termination of the CED scheme [11]. Ideally, this would also entail a withdrawal implementation plan. The third challenge concerns the economies of scale in the management of CED schemes and the difficulties small countries may have in applying CED schemes because of the associated costs and monitoring mechanisms [20].

Discussion

The objective of this study was to identify and describe the challenges that payers and manufacturers might face when assessing the desirability of, choosing the research design for, implementing, and evaluating CED schemes for MDs. We identified 20 distinct challenges that are associated with CED schemes for MDs. Most of these challenges are not specific for MDs; however, five are, as they relate directly to the characteristics of MDs. These challenges concern deciding on whether a CED scheme is required, understanding the relevant uncertainties and risks, identifying meaningful outcomes, defining an adequate duration for a scheme, and market entry of new technologies during the existence of a scheme. The majority of studies discussed challenges with CED schemes in the context of applied CED schemes for MDs. Generally, studies discussed challenges with CED schemes for all types of technologies and only few specifically discussed them for MDs. Most of the challenges that relate to the characteristics of MDs were discussed by Rothery et al. (2017).

These results suggest that the challenges associated with CED schemes for MDs and the relationship between these challenges and the characteristics of MDs are infrequently researched. Although the many similarities between challenges with CED schemes for MDs and other types of technologies, such as pharmaceuticals, may have reduced the need for research in this area, these results can still be considered remarkable given the considerable decision uncertainty associated with coverage and reimbursement of MDs and the direct relevance of CED schemes in this context. Our finding that challenges with CED schemes for MDs are infrequently researched is further illustrated by the fact that this, to our knowledge, is the first systematic review of the literature that focuses specifically on this topic. Although we consider this a strength, some limitations also deserve attention. Firstly, CED schemes go under many different names and some schemes that are applied for MDs may have a confidential nature [12,14,21]. Consequently, we cannot rule out the possibility that there are challenges associated with CED schemes for MDs that we have not identified and described in our review. We also cannot rule out the possibility that there are CED schemes for MDs that are not identified and mentioned in our review (Table 1), as we excluded articles that merely reported on the characteristics, processes, and/or results of applied CED schemes. However, this limitation does not affect our main findings. Secondly, we synthesised our results in a qualitative rather than a quantitative review. Hence, our review does not provide information about the extent to which the characteristics of MDs impact on the challenges associated with CED schemes, nor about the frequency and intensity with which the challenges occur in practice. Finally, some of the studies included in our review applied a combination of methods to gain insight into challenges associated with CED schemes that are not technology specific. For example, Carbonneil et al. (2009), Claxton et al. (2012), and Brügger (2014) have supplemented their review of the literature with one or more case studies, a survey, and/or interviews with experts. Future research may be aimed at gaining additional insight into the challenges specifically associated with CED schemes for MDs, for example, by conducting interviews with payers who are experienced in applying these schemes.

Future research may also be aimed at validating and deepening the understanding of the identified challenges and examining possible differences in (the intensity of) challenges associated with CED schemes for different types of MDs, i.e. implantable, diagnostic, and therapeutic devices. Interviews may, for example, also provide insight into whether high upfront investment costs pose more of a challenge than rapid incremental innovation for CED schemes for diagnostic devices such as PET scans. Furthermore, we would like to note that the challenges were mainly described from the perspective of payers and manufacturers of MDs, even though some of the identified challenges with CED schemes directly relate to the role of other stakeholders, such as patients and physicians. Future research may be aimed at obtaining insight into possible additional challenges that are associated with CED schemes for MDs, e.g., from the perspective of other stakeholders, that are not yet identified and discussed in this review, yet may also be considered relevant for those who (intend to) apply CED schemes for MDs.

To improve a CED scheme's chance of success, it is considered important that payers and manufacturers of MDs have insight into and address the challenges described in this review. However, the challenges associated with evaluating CED schemes for MDs make it clear that there is little evidence to support the claimed benefits of CED schemes [23]. Indeed, studies infrequently report on the outcomes of CED schemes and little is known about their impact on patients' access to technologies and the reduction of costs in the long run [20,23,24]. Public sharing of information about the outcomes of applied schemes may reduce the overlap in CED schemes for MDs between countries as, for example, observed for the USA, Australia, Canada (Ontario), Germany, and Spain. These countries have all applied a CED scheme for PET scans for diagnosis of dementia and/or various cancer types. Public sharing of information about the outcome of applied schemes and the way in which various stakeholders have addressed the challenges they faced when applying (or participating in) CED schemes for MDs may further improve a CED scheme's chance of success. For example, by

increasing cross-country learning, reducing the costs of individual schemes, improving the design of future schemes, and increasing trust amongst payers that CED schemes are a valuable option.

Conclusions

The results of this study indicate that there are at least 20 challenges that payers and manufacturers might face when applying CED schemes for MDs. Some of these challenges are specific to MDs, given their distinct characteristics, but many are relevant more generally. The MD-specific challenges concern deciding on whether a CED scheme is required, understanding the relevant uncertainties and risks, identifying meaningful outcomes, defining an adequate duration for a scheme, and market entry of new technologies. It is considered important that payers and manufacturers of MDs are aware of, and where possible proactively address, these challenges when considering the use of a CED scheme, also to improve its chances of success and final reimbursement decisions. Public sharing of information about the outcomes of applied schemes and the way in which various stakeholders have addressed the challenges they faced when applying (or participating in) CED schemes for MDs may further improve their future use and contribute to better decision making in health care.

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Competing interests

None declared.

Ethical approval

This study is part of the EU Horizon 2020 COMED project that has been reviewed and approved by the Bocconi University Ethics Committee (protocol number: 0068538, approved on May 8, 2018).

CRediT authorship contribution statement

Vivian Reckers-Droog: Methodology, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Carlo Federici:** Methodology, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Werner Brouwer:** Methodology, Supervision, Writing - review & editing. **Michael Drummond:** Methodology, Supervision, Writing - review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.hlpt.2020.02.006.

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