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IMPROVING THE METHODS FOR THE ECONOMIC EVALUATION OF MEDICAL DEVICES

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ABSTRACT

Medical devices (MDs) have distinctive features, such as incremental innovation, dynamic pricing, the learning curve and organisational impact, that need to be considered when they are evaluated. This paper investigates how MDs have been assessed in practice, in order to identify methodological gaps that need to be addressed to improve the decision-making process for their adoption.

We used the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist supplemented by some additional categories to assess the quality of reporting and consideration of the distinctive features of MDs. Two case studies were considered: transcatheter aortic valve implantation (TAVI) representing an emerging technology and implantable cardioverter defibrillators (ICDs) representing a mature technology. Economic evaluation studies published as journal articles or within Health Technology Assessment reports were identified through a systematic literature review. A total of 19 studies on TAVI and 41 studies on ICDs were analysed. Learning curve was considered in only 16% of studies on TAVI. Incremental innovation was more frequently mentioned in the studies of ICDs, but its impact was considered in only 34% of the cases. Dynamic pricing was the most recognised feature but was empirically tested in less than half of studies of TAVI and only 32% of studies on ICDs. Finally, organisational impact was considered in only one study of ICDs and in almost all studies on TAVI, but none of them estimated its impact.

By their very nature, most of the distinctive features of MDs cannot be fully assessed at market entry. However, their potential impact could be modelled, based on the experience with previous MDs, in order to make a preliminary recommendation. Then, well-designed post-market studies could help in reducing uncertainties and make policymakers more confident to achieve conclusive recommendations.

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KEY WORDS: medical devices; MedtecHTA; economic evaluation analysis; health technology assessment

1. INTRODUCTION

The rationale behind the MedtecHTA project is as follows: (i) medical devices (MDs) are characterised by distinctive features that are less frequently found in drugs and (ii) these features need to be considered when MDs are assessed in order to help decision-makers formulate appropriate recommendations (Drummond *et al*., 2009; Taylor and Iglesias, 2009). The most important specific characteristic associated with the use of MDs is the *learning curve*, which can be related to the following: (i) the operator's skills and experience with the delivery of the new procedure and with the selection of patients (e.g. patients eligible to new mini-invasive surgical procedures need to be appropriately identified and selected in order to maximise the performance of the new technology) and (ii) the scale, that is the higher the volume of procedures performed, the better the performance of the device, the health outcomes and the overall provider's productivity and procedure costs.

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These considerations imply that assessing MDs is more challenging than assessing drugs, both because of the level of uncertainty concerning costs and outcomes and because of the time when they will accrue.

The second characteristic is *incremental innovation*, that is the constant product modifications that devices often undergo, which can impact clinical efficacy/effectiveness and costs (Ciani *et al*., 2015a). Incremental innovation is a challenge when the source of clinical evidence mainly derives from experimental studies such as randomised controlled trials (RCTs) because, by the time the RCT is completed, the device is often obsolete and new versions are already in use. The implication is that MDs often never reach a steady state, which makes the timing of the assessment a challenge. A further aspect is *dynamic pricing*, due to the regulation and procurement of MDs. MDs typically show rapid decreases in their price due to incremental innovation and to the market entry of competitor products claiming equivalence without the same evidence base, which clearly impacts the calculation of the incremental cost-effectiveness ratio (ICER). Again, this consideration raises the level of uncertainty in assessing MDs, which needs to be managed by decision-makers when coverage and reimbursement policies are being considered. The last feature is *organisational impact*, which for MDs becomes relevant because their adoption in clinical practice frequently requires substantial organisational investments and/or adaptations (e.g. new capital equipment, creation of multidisciplinary teams and need for supervision). Here again the scale becomes relevant; in addition to its impact on the learning curve of providers and operators, the scale often represents a regulatory hurdle that affects the organisation because, for several MDs, hospitals are required to deliver a minimum number of procedures to become authorised centres (BCIS and SCTS, 2009; College voor Zorgverzekeringen, 2011; Centers for Medicare and Medicaid Services, 2012; INESSS, 2012). Yet, when the delivery of new procedures entails big capital investments (Tarricone *et al*., 2008), it is in the interest of providers to increase the number of procedures so as to maximise economies of scale. This may impact the cost-effectiveness of the device in actual use. In addition, these investments often are unrecoverable costs that need to be considered in before deciding whether the MD is worth introducing in clinical practice (see the paper in this supplement by Rothery *et al*., 2017).

In order to capture these features, methods to conduct economic evaluation (EE) of MDs might need to encompass a wider range of approaches than those traditionally used for assessing drugs. Therefore, the MedtecHTA project has investigated how MDs are currently assessed, whether there are gaps to be addressed and whether there are recommendations to be provided to the scientific community. As a result of other research conducted in the project, Ciani *et al*. (2015b) found that, although many Health Technology Assessment (HTA) bodies had adopted HTA-specific approaches for MDs, these were largely organisational or procedural in nature rather than implying different methods. As to non-European Union countries, only the Brazilian agency had adopted methodological guidelines specific to MDs, while in Europe the National Institute for Health and Clinical Excellence (NICE) in UK had developed the Medical Technologies Evaluation Programme (NICE, 2011) for assessing new devices and diagnostics.

In a further paper, included in this supplement (Ciani *et al*., 2017), a sample of HTA reports were analysed in order to assess whether there were any key differences in the methods applied in the HTA of devices as compared with drugs. They found that there were several differences in the types of clinical studies forming the basis for the HTAs, how the health problem and use of the technology were considered, the description and technical characteristics of the technology and the consideration of the organisational aspects of the use of the technology.

This paper builds on these findings by gathering more detailed evidence on how MDs are actually assessed by HTA agencies and by analysts conducting EEs published in the general literature. The objective was to identify the methodological gaps and to provide recommendations on how to improve the assessment of MDs in the future as reported by Tarricone *et al*. (2017) in this supplement.

2. METHODS

2.1. Framework

No specific assessment tool currently exists to review economic studies on MDs. We therefore used the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (Husereau *et al*. 2013)

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but included additional items specifically targeted to analyse and compare EEs and HTA reports of MDs. More specifically, to the original CHEERS 24-item checklist, we added four items to analyse whether and how the distinctive features of MDs had been considered while assessing the technologies. These were the learning curve, incremental innovation, dynamic pricing and organisational impact. For each of the four features, we investigated whether they had been considered or not and, if considered, how this was done, that is whether they were *formally considered* (i.e. the authors generically referred to them in the document, with no attempt to measure their impact on final results/recommendations) or *substantially measured* (i.e. the impact was empirically investigated). Finally, some of the original 24 items of the CHEERS checklist were divided into sub-items and made more granular, in order to identify the types of EEs performed, the sources of treatment effects, utilities, resource consumption and costs, the types of costs, the types of modelling and whether the findings had been presented in terms of incremental costs and outcomes and a final recommendation issued. Thus, the adapted CHEERS checklist consists of 28 items grouped into the following sections: title and abstracts, introduction, methods, results, discussion, other and the distinctive features of MDs (Table I).

The checklist was used as a protocol for data extraction to analyse how MDs were assessed in the studies considered.

2.2. Case studies

Two categories of cardiac devices were chosen for the case studies. Cardiac devices have been thoroughly investigated throughout the MedtecHTA project for several reasons. First, the cardiovascular sector represents the second largest device sector—after *in vitro* diagnostics—for sales and market share (Evaluate Group, 2016). Its substantial impact on healthcare budgets has spurred a large number of EEs, generating a rich literature. Secondly, the cardiovascular area is characterised by a fast pace of innovation, both breakthrough and incremental (Levin, 2015). Because the relevance of some of the key features of MDs (e.g. incremental innovation and learning curve) depends upon the phase of the life cycle in which they are in, we identified one recently introduced device (i.e. transcatheter aortic valve implantation (TAVI)) and a mature technology, characterised by incremental innovation (i.e. implantable cardioverter defibrillators (ICDs)). Finally, the participation of the European Society of Cardiology (ESC) in the MedtecHTA Consortium was the natural incentive to select cardiac devices, given the technical and clinical advice that could be provided.

2.2.1. Transcatheter aortic valve implantation. Transcatheter aortic valve implantation is emerging as an alternative treatment option to surgery for symptomatic severe aortic stenosis (SSAS), the most frequent valvulopathy in Western countries (Vahanian *et al*., 2008). The valve implantation is achieved by a catheter technique through two main access routes, transfemoral and transapical. The target population is represented by patients affected by SSAS, aged 75 or more, who are not eligible (i.e. inoperable) or are at high risk for conventional surgery. TAVI was Conformité Européene (CE) marked and introduced into clinical practice in 2007, while in the USA, the Food and Drug Administration (FDA) approved it for inoperable patients in 2011, after publication of the results of the first RCT, PARTNER Cohort B (which enrolled a cohort involving inoperable patients) (Leon *et al*., 2010; Smith *et al*., 2011).

2.2.2. Implantable cardioverter defibrillators. We investigated both single-chamber and dual-chamber ICDs. First introduced in the market in the 1980s, both types of ICDs provide defibrillation shocks to correct heart rhythm dysfunctions. The target populations for ICDs are patients at increased risk of sudden cardiac death as a consequence of ventricular arrhythmias despite receiving optimal medical therapy (OMT), people with heart failure as a result of left ventricular systolic dysfunction or cardiac dissynchrony despite receiving OMT and people with both conditions (Colquitt *et al*., 2014). ICDs have been investigated in numerous RCTs in the last decades.

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Table I. Framework for analyses of economic evaluation analyses and health technology assessment reports of medical devices

Item no.	Item	Possible values	Definition
Title and abstract			
1	Title	Open-ended	
2	Abstract	Open-ended	
Introduction			
3	Background and objectives	Open-ended	
Methods			
4	Target population and subgroups	Open-ended	
5	Setting and location	Open-ended	
6	Study perspective	Society	All costs and benefits for which the entire society is accountable no matter who bears them
		NHS	All costs and benefits relevant for which the NHS is accountable
		Third-party payer	All costs and benefits relevant for which the third-party payer is accountable (e.g. regional authority and district health authority)
		Provider	All costs and benefits relevant for which the single provider is accountable (e.g. hospital)
7	Comparators	Open-ended	
8	Time horizon	Open-ended	
9	Discount rate		
9a	Discount rate for benefits	Yes, No, Not reported	
9b	Discount rate for costs	Yes, No, Not reported	
10	Choice of health outcomes		
10a	Form of economic evaluation (declared by the authors)	Cost description	
		Cost analysis	
		Cost minimisation	
		Cost-effectiveness	
		Cost–utility	Full economic evaluation where consequences are measured in QALYs
		Cost–benefit	Full economic evaluation where both costs and outcomes are measured in monetary terms
		Cost consequence	Full economic evaluation that does not put all of the costs and benefits in the same units
10b	Outcome measure	LYG	Life years gained
		QALY	Quality-adjusted life years
		Surrogates	Intermediate endpoints that are used to substitute and predict final outcomes
11	Measurement of effectiveness		
11a	Number of sources of treatment effects		
11b	Sources of treatment effects in single-study-based economic evaluations	RCTs, non-RCTs, observational studies, administrative data, manufacturer, other, not reported	
11c	Sources of treatment effects in synthesis-based economic evaluations	RCTs, non-RCTs, observational studies, administrative data, manufacturer, other, not reported	
12	Measurement and valuation of preference-based outcomes (if applicable)	RCTs, non-RCTs, observational studies, evidence synthesis, administrative data, other, not reported	

(*Continues*)

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Table I. (Continued)

Item no.	Item	Possible values	Definition
13	Estimating resources and costs		
13a	Sources of resource consumption in single-study-based economic evaluations	RCTs, non-RCTs, observational studies, administrative data, production costs, other, not reported	
13b	Sources of resource consumption in synthesis-based economic evaluations	RCTs, non-RCTs, observational studies, evidence synthesis, administrative data, production costs, other, not reported	
13c	Sources of monetary values to estimate costs in single-study-based economic evaluations	RCTs, non-RCTs, observational studies, evidence synthesis, administrative data, production costs, official price/tariff list, manufacturer, other, not reported	
13d	Sources of monetary values to estimate costs in synthesis-based economic evaluations	RCTs, non-RCTs, observational studies, evidence synthesis, administrative data, production costs, official price/tariff list, manufacturer, other, not reported	
13e	Type of costs	Direct healthcare costs	Include device, consumables, procedure, drugs, hospital stay and other direct healthcare resources
		Direct non-healthcare costs	Include transportation, informal care and other non-healthcare direct costs
		Productivity losses	Loss of productivity due to patient's absence from workplace
14	Currency, price date and conversion		
14a	Currency	Reported, Not reported	
14b	Price date	Reported, Not reported	
14c	Conversion	Reported, Not reported	
15	Choice of model		
15a	Model design	Decision analysis/decision tree, Markov, discrete event simulation, micro-simulation, not model based	
15b	Discussion on choice of model	Reported, Not reported	
15c	Figure of model structure	Reported, Not reported	
16	Assumptions	Reported, Not reported	
17	Analytical methods	Reported, Not reported	
Results			
18	Study parameters	Reported, Not reported	
19	Incremental costs and outcomes		
19a	Incremental costs	Reported, Not reported	Difference in costs between two alternative technologies
19b	Incremental effectiveness	Reported, Not reported	Difference in effectiveness between two alternative technologies
19c	ICER	Reported, Not reported	Ratio of incremental cost to incremental effectiveness
19d	WTP threshold	Reported, Not reported	Maximum amount that society is willing to pay for a unit of health gain (e.g. QALY and LYG)
19e	Cost-effectiveness acceptability curves	Reported, Not reported	Curve representing the distribution of the ICERs below the WTP threshold value for all possible threshold values
19f	Final recommendation	Reported, Not reported	

(*Continues*)

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Table I. (Continued)

Item no.	Item	Possible values	Definition
19g	Policy recommendation	Adopt Reject Only in research Approval with research Other policy recommendation	
19h	Technical conclusion	Costhy-effective, Not cost-effective	
20	Characterising uncertainty		
20a	Uncertainty in single-study-based economic evaluations	One-way (deterministic) sensitivity analysis	Estimate of the impact of single parameters on the results, obtained by varying the variables' values one at a time
		Multi-way (probabilistic) sensitivity analysis	Estimate of the impact of more than one parameter on the results, obtained by varying simultaneously more than one variable values
		Scenario analysis	Subset of potential multi-way analysis obtained by identifying several scenarios (e.g. best case, most optimistic and most pessimistic)
		Threshold analysis	Analysis based on the identification of critical value(s) of parameters central to the decision
		No sensitivity analysis	No analysis performed to assess uncertainty of parameters
		Not reported	
20b	Uncertainty in synthesis-based economic evaluations	One-way (deterministic) sensitivity analysis, multi-way (probabilistic) sensitivity analysis, scenario analysis, threshold analysis, no sensitivity analysis, not reported	
21	Characterising heterogeneity (if applicable)	Reported/Not reported/Not applicable	
Discussion			
22	Study findings, limitations, generalisability and current knowledge	Reported, Not reported	
Other			
23	Source of funding	Government, Industry, Self-funded, Not reported	
24	Conflicts of interest	Conflicts of interest reported, No conflicts of interest reported, Not reported	
Medical devices' distinctive features			
25	Learning curve	Formal	Empirically estimated in sensitivity analysis
		Substantial	Only mentioned in the text
		Not considered	
26	Incremental innovation	Formal, Substantial, Not considered	
27	Dynamic pricing	Formal, Substantial, Not considered	
28	Organisational impact	Formal, Substantial, Not considered	

ICER, incremental cost-effectiveness ratio; LYG, life year gained; NHS, National Health Service; QALY, quality-adjusted life year; RCT, randomised controlled trial; WTP, willingness to pay.

2.3. Literature search

A systematic review of full texts of economic analyses on TAVI and ICDs published up until December 2014 was conducted. We searched for both journal articles and economic analyses published within HTA reports. We searched the University of York's Centre for Reviews and Dissemination HTA Database and

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National Health Service Economic Evaluation Database (http://www.crd.york.ac.uk/CRDWeb/) and PubMed. We used as keywords, in all fields, the name of the investigated technologies or their acronyms, combined with one of the following keywords: 'cost*', 'cost-effective*', 'economic evaluation*', 'HTA' or 'health technology assessment', with no restriction on language or year of publication. In addition, we performed manual electronic browsing (i.e. googling) using the same keywords as in the general search. Finally, we searched all the references cited in the retrieved documents. Systematic literature reviews on the cost-effectiveness of the selected devices were excluded, although they were analysed to check the completeness of the identified sources (see the list of papers in the specific sections of the references.) HTA reports that did not contain any economic analysis were also excluded but were analysed to understand the nature of the information they provided. Non-English documents were translated into English. Two researchers independently reviewed the full text of retrieved documents and extracted the information included in the framework (Table I).

3. RESULTS

3.1. Results of the literature search

The results of the literature search are summarised in the Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram shown in Figure 1. For TAVI, we retrieved 75 documents overall: 56 documents published by HTA agencies, of which seven contained some form of EE, 14 published papers and 5 systematic reviews on cost-effectiveness of TAVI. Once exclusion criteria were applied, we finally obtained and reviewed 21 documents published between 2009 and 2014. Because two studies were published both within HTA reports (Neyt *et al*., 2011; Sehatzadeh *et al*., 2012) and as journal articles (Neyt *et al*., 2012; Doble *et al*., 2013), the latter was excluded in order to avoid double counting. Therefore, the results refer to 19 studies.

For ICDs, we identified 53 relevant documents: 12 HTA reports, of which seven included EEs, 36 articles and 5 systematic reviews on cost-effectiveness of ICDs. The latter were excluded, together with five HTAs not including an economic analysis, resulting in a final list of 43 documents published between 1990 and 2014. Two studies (McGregor and Chen, 2004; Neyt *et al*., 2008) reporting on previously published HTAs (McGregor and Chen, 2003; Van Brabandt *et al*., 2006) were excluded. Therefore, the results relate to 41 studies.

The time trend of publications reveals that for a breakthrough innovative device like TAVI, the vast majority of EEs (86%) were not published until sometime after launch (i.e. since 2012, 5 years after market approval), while the vast majority of HTA reports with no economic analysis (84%) (i.e. focusing on clinical aspects only) were conducted earlier (i.e., before the end of 2012) (Table II). Although it is true that publication of journal articles takes time and this might generate a problem of time lag in publication, from these findings, it is clear that the diffusion of the innovative device occurred in the absence of economic evidence, given that more than 34 000 implants had already been performed in Europe between 2007 and 2011 (Mylotte *et al*., 2013). Contrasting results were found for the mature technology (ICDs), where only 10% of HTA reports did not contain any economic analysis.

3.2. Methods for economic evaluation used in the reviewed studies

Table III provides a summary of the information extracted from the retrieved documents.

For both technologies, the majority of studies were conducted from a national health service perspective (37% for TAVI and 44% for ICDs) or third-party payer perspective (37% for TAVI and 27% for ICDs). The only studies adopting the provider perspective were two cost descriptions of TAVI performed by the McGill University Health Centre (McGregor and Esfandiari, 2009; Sinclair *et al*., 2013). All studies on TAVI and 98% on ICDs considered only direct healthcare costs (mainly the cost of the device, procedure, hospitalisation and follow-up) regardless of whether they were published as journal articles or HTA reports. Costs related to

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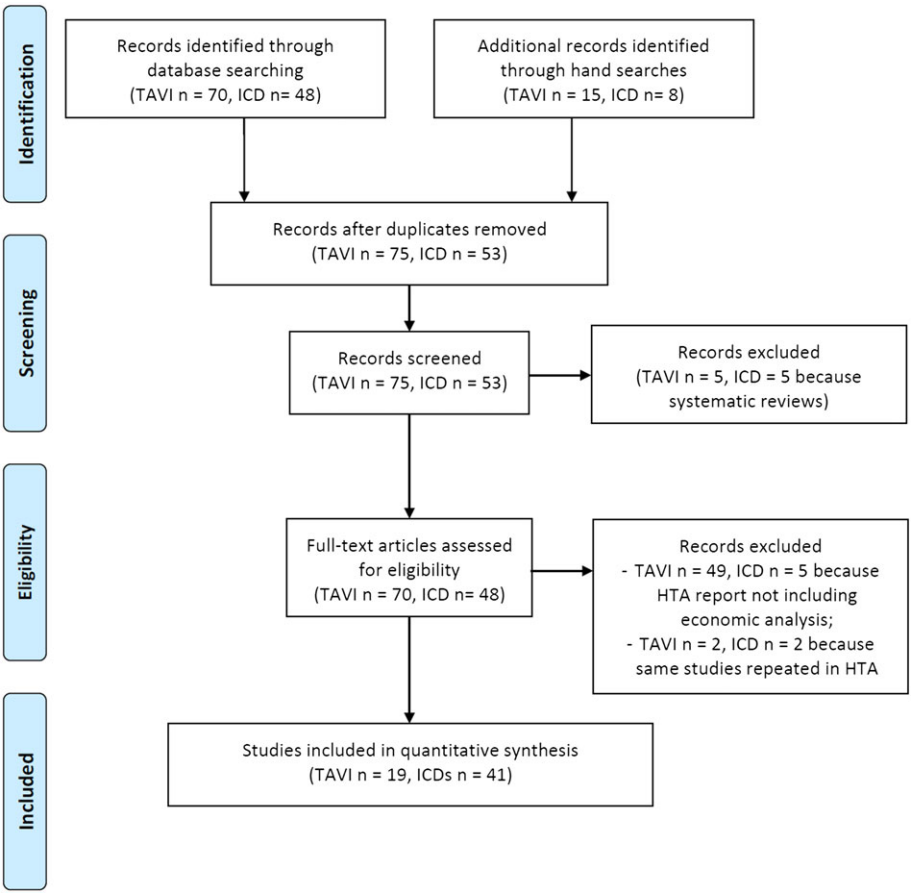

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses diagram of the systematic review. ICD, implantable cardioverter defibrillator; TAVI, transcatheter aortic valve implantation [Colour figure can be viewed at wileyonlinelibrary.com]

transportation and productivity losses were mentioned only in 5% of the studies on ICDs, even though the authors declared they adopted a societal perspective in 16% of the analyses on TAVI and 29% of the analyses on ICDs.

For TAVI, cost–utility analysis was by far the most common type of EE, being performed in 88% of the studies. Indeed, quality-adjusted life years (QALYs) were used either as the sole outcome measure in 35% of the studies or in combination with life years gained (LYG) in 53% of the economic analyses. This result does not match with what was reported by the authors, who declared they performed a cost–utility only in 21% of the cases and cost-effectiveness analysis in 84%. The incoherence between the type of analysis declared by the authors and the one actually performed may be attributable to the consolidated use of the term "cost-effectiveness" in the US literature, in cases when both LYG and QALYs are computed. This is less evident for ICDs, where cost-effectiveness is the most frequent type of analysis both performed (75% of studies) and declared (90%) by the analysts. Intermediate outcome measures were never used.

As for the sources of treatment effects, all the EEs of TAVI published within HTA reports and 75% of journal articles are single-study analyses based on PARTNER, the first and only RCT available at the time of the economic studies. The remaining analyses were based on real-world (RW) registries, combined, in one case, with data from the RCT. The source of clinical evidence for ICDs is more diverse, because numerous trials had been performed by the time the EEs were published. For this device, most EEs (86% of HTA reports and 74% of journal articles) were synthesis-based and relied mainly on RCTs and observational studies. RCTs

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Table II. Time trends of publications

	ICD		TAVI	
	HTA reports with economic analysis and EEs published as journal articles	HTA without economic analysis	HTA reports with economic analysis and EEs published as journal articles	HTA without economic analysis
1990	1			
1991				
1992	2			
1993				
1994				
1995	1			
1996	1			
1997	1			
1998	1			
1999				
2000		1		
2001	3	1		
2002	3			
2003	1			
2004	3			
2005	4	2		
2006	6			
2007	2			
2008	2			7
2009	4		1	4
2010	3		1	8
2011	2		1	10
2012			7	12
2013	2		9	7
2014	1	1	2	1
Total	43	5	21	49

EE, economic evaluation; HTA, health technology assessment; ICD, implantable cardioverter defibrillator; TAVI, transcatheter aortic valve implantation.

also represent the main source also for utilities and resource consumption. More specifically, utilities for TAVI were estimated through either PARTNER when available or through the New York Heart Association class utilities (other sources in Table III) before the publication of PARTNER. As for resource consumption, observational studies were also frequently used for both technologies, in both single-study-based and synthesis-based analyses. For ICDs, other sources (e.g. authors' own assumptions, estimates, unpublished data, interviews and expert opinion) were also used to derive clinical and economic evidence.

Three quarters of the studies used some modelling, principally Markov models and decision trees. In addition, two studies on ICDs used discrete event simulation. In almost all the analyses, the analysts reported the assumptions underlying the model and the analytical methods and provided a scheme of the model. The choice of the model was discussed in 71% of the studies on TAVI but only in 7% of ICDs. Time horizon was longer than 5 years in 43% of studies on TAVI and 78% on ICDs. In half of the studies of ICDs, model time horizons reached the upper limits of 20 years and lifetime (that is considered equivalent to 40 years). When the time horizon was longer than 1 year, costs and benefits were discounted, the most common rates being 5%, 3.5% and 3%.

The great majority of the studies (89% on TAVI and 78% on ICDs) performed some form of sensitivity analysis, mainly deterministic and probabilistic, sometimes combined with threshold or scenario analysis. Sensitivity analyses considered clinical parameters (e.g. mortality rates, follow-up events and hospital length of stay), utilities or economic-related aspects (e.g. price of devices and of procedures, procedural time, probability of implant failure, battery longevity, discount rates and time horizon).

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Table III. Summary of results

No.	Item	Value	TAVI (*N*)	TAVI (%)	ICD (*N*)	ICD (%)
Title and abstract						
1	Title		19	100	41	100
2	Abstract		19	100	41	100
Introduction						
3	Background and objectives		19	100	41	100
Methods						
4	Target population and subgroups	Inoperable patients	10	53		
		High-risk patients	7	37		
		Not applicable	2	11		
5	Setting and location	Argentina	0	0	1	2
		Australia	0	0	1	2
		Belgium	1	5	2	5
		Brazil	1	5	2	5
		Canada	5	26	7	17
		France	0	0	0	0
		Germany	0	0	1	2
		Japan	0	0	1	2
		South Africa	1	5	0	0
		Spain	1	5	0	0
		The Netherlands	0	0	2	5
		UK	5	26	3	7
		UK and France	0	0	1	2
		USA	5	26	20	49
6	Study perspective	Society	3	16	12	29
		NHS	7	37	18	44
		Third-party payer	7	37	11	27
		Provider	2	11	0	0
7	Comparators	MM	10	53		
		AVR	4	21		
		Mixture of MM and AVR	3	16		
		No comparator	2	11		
		OMT			35	85
		No treatment			6	15
8	Time horizon	1–5 years	7	33	7	17
		>6 years	4	19	11	27
		Lifetime	5	24	21	51
		Not reported	3	14	2	5
9	Discount rate					
9a	Discount rate for benefits	Yes	12	71	33	80
		No	3	18	8	20
		Not reported	2	12		
9b	Discount rate for costs	Yes	13	68	41	100
		No	4	21		
		Not reported	2	11		
10	Choice of health outcomes					
10a	Form of economic evaluation (declared by the authors)	Cost description	2	11	1	2
		Cost analysis	0	0	0	0
		Cost minimisation	0	0	0	0
		Cost-effectiveness	16	84	37	90
		Cost–utility	4	21	5	12
		Cost–benefit	0	0	2	5
		Cost consequence	0	0	0	0
10b	Outcome measure	LYG	10	59	30	75
		QALY	15	88	22	55
		Monetary outcome	0	0	2	5
		Surrogates	0	0	0	0
11	Measurement of effectiveness					
11a		Single-study-based HTA report	7	100	1	14

(*Continues*)

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Table III. (Continued)

No.	Item	Value	TAVI (*N*)	TAVI (%)	ICD (*N*)	ICD (%)
	Number of sources of treatment effects	Synthesis-based HTA report	0	0	6	86
		Single-study-based journal article	9	75	9	26
		Synthesis-based journal article	3	25	25	74
11b	Sources of treatment effects in single-study-based economic evaluations	RCTs	12	86	11	73
		Non-RCTs	0	0	0	0
		Observational studies	1	7	4	27
		Administrative data (mortality registry)	1	7	0	0
		Manufacturer report	0	0	1	7
		Other (targeted literature search)	2	14	0	0
		Not reported	0	0	0	0
11c	Sources of treatment effects in synthesis-based economic evaluations	RCTs	1	33	19	76
		Non-RCTs	0	0	0	0
		Observational studies	3	100	12	48
		Evidence synthesis	0	0	0	0
		Administrative data	0	0	0	0
		Manufacturer report	0	0	2	8
		Other (published literature)	0	0	2	8
		Not reported	0	0	0	0
12	Measurement and valuation of preference-based outcomes	RCTs	6	35	18	45
		Non-RCTs	0	0	0	0
		Observational studies	1	6	8	20
		Evidence synthesis	0	0	0	0
		Administrative data (Medical Expenditure Panel Survey)	3	18	0	0
		Other (New York Heart Association class utilities, published and unpublished literature, authors' estimates)	7	41	6	15
		Not reported	2	12	0	0
13	Estimating resources and costs					
13a	Sources of resource consumption in single-study-based economic evaluations	RCTs	6	38	7	47
		Non-RCTs	0	0	0	0
		Observational studies	3	19	5	33
		Administrative data (Ontario Case Costing Initiative, Ontario Health Insurance Plan, private insurance billing data and Health Care Financing Administration Medicare Provider Analysis and Review)	2	13	1	7
		Hospital costs	4	25	0	0
		Other	0	0	0	0
		Not reported	4	25	0	0
13b	Sources of resource consumption in synthesis-based economic evaluations	RCTs	0	0	8	31
		Non-RCTs	0	0	0	0
		Observational studies	1	33	10	38
		Evidence synthesis (review of published reports)	0	0	1	4
		Administrative data (Medical Expenditure Panel Survey)	0	0	1	4
		Hospital costs	0	0	2	8
		Other (experts' opinion and unpublished data)	2	67	8	31
		Not reported	0	0	1	4
13c	Sources of monetary values to estimate costs in single-study-based economic evaluations	RCTs	0	0	1	7
		Non-RCTs	0	0	0	0
		Observational studies	0	0	4	27
		Evidence synthesis	0	0	0	0
		Administrative data (government or private health insurance claims data, Ontario Case Costing Initiative and Ontario Health Insurance Plan)	5	31	4	27
		Hospital costs	8	50	0	0
		Official price/tariff list	7	44	6	40

(*Continues*)

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Table III. (Continued)

No.	Item	Value	TAVI (*N*)	TAVI (%)	ICD (*N*)	ICD (%)
		Manufacturer	1	6	2	13
		Other (published reports or literature)	2	13	0	0
		Not reported	0	0	0	0
13d	Sources of monetary values to estimate costs in synthesis-based economic evaluations	RCTs	0	0	2	8
		Non-RCTs	0	0	0	0
		Observational studies	0	0	3	12
		Evidence synthesis	0	0	0	0
		Administrative data (Ontario Case Costing Project, Medical Expenditure Panel Survey and Brazilian Ministry of Health database)	0	0	5	19
		Hospital costs	0	0	6	23
		Official price/tariff list	3	100	12	46
		Manufacturer	0	0	3	12
		Other (unpublished data)	0	0	3	12
		Not reported	0	0	0	0
13e	Type of costs	Direct healthcare costs				
		Device	15	79	40	98
		Consumables	3	16	38	93
		Procedure	16	84	40	98
		Drugs	4	21	15	37
		Hospital stay	15	79	39	95
		Other	18	95	14	34
		Direct non-healthcare costs				
		Transportation	0	0	2	5
		Informal care	0	0	0	0
		Other	0	0	2	5
		Productivity losses	0	0	2	5
14	Currency, price date, and conversion					
14a	Currency	Reported	19	100	41	100
		Not reported	0	0		0
14b	Price date	Reported	13	68	32	78
		Not reported	6	32	9	22
14c	Conversion	Reported	9	47	27	66
		Not reported	10	53	14	34
15	Choice of model					
15a	Model design	Decision tree	6	32	4	10
		Markov model	12	63	24	59
		Discrete event simulation	0	0	2	5
		Micro-simulation	0	0	0	0
		Not model based	5	26	11	27
15b	Discussion on choice of model	Reported	10	71	2	7
		Not reported	4	29	28	93
15c	Figure of model structure	Reported	14	100	23	74
		Not reported	0	0	8	26
16	Assumptions	Reported	12	86	30	97
		Not reported	2	14	1	3
17	Analytical methods	Reported	15	88	38	95
		Not reported	2	12	2	5
Results						
18	Study parameters	Reported	11	65	41	100
		Not reported	6	35	0	0
19	Incremental costs and outcomes					
19a	Incremental costs	Reported	16	84	40	98
		Not reported	3	16	1	2
19b	Incremental effectiveness	Reported	15	88	40	100
		Not reported	2	12		
19c	ICER	Reported	16	84	40	100

(*Continues*)

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Table III. (Continued)

No.	Item	Value	TAVI (*N*)	TAVI (%)	ICD (*N*)	ICD (%)
		Not reported	3	16		
19d	WTP threshold	Reported	16	84	18	45
		Not reported	3	16	22	55
19e	Cost-effectiveness acceptability curves	Reported	9	53	8	20
		Not reported	8	47	32	80
19f	Final recommendation	Reported	19	100	38	93
		Not reported	0	0	3	7
19g	Policy recommendation	Adopt/reject	1	14	1	14
		Only in research	0	0	0	0
		Approval with research	0	0	0	0
		Other policy recommendation	0	0	0	0
19h	Technical conclusion					
	TAVI vs MM	Cost-effective	12	92		
		Dominant	0	0		
		Dominated	0	0		
		Not cost-effective	1	8		
	TAVI vs AVR	Cost-effective	3	33		
		Dominant	2	22		
		Dominated	3	33		
		Not cost-effective	1	11		
	ICD vs OMT	Cost-effective			22	67
		Dominant			0	0
		Dominated			0	0
		Not cost-effective			11	33
	ICD vs no therapy	Cost-effective			4	100
		Dominant			0	0
		Dominated			0	0
		Not cost-effective			0	0
20	Characterising uncertainty					
20a	Uncertainty in single-study-based economic evaluations	One-way (deterministic) sensitivity analysis	11	69	8	53
		Multi-way (probabilistic) sensitivity analysis	7	44	3	20
		Scenario analysis	0	0	2	13
		Threshold analysis	0	0	0	0
		No sensitivity analysis	2	13	2	13
		Not reported	0	0	1	7
20b	Uncertainty in synthesis-based economic evaluations	One-way (deterministic) sensitivity analysis	3	100	18	69
		Multi-way (probabilistic) sensitivity analysis	3	100	8	31
		Scenario analysis	2	67	1	4
		Threshold analysis	2	67	0	0
		No sensitivity analysis	0	0	1	4
		Not reported	0	0	5	19
21	Characterising heterogeneity	Reported	1	5	21	51
		Not reported	0	0	18	44
		Not applicable	18	95	2	5
Discussion						
22	Study findings, limitations, generalisability and current knowledge	Reported	15	79	34	83
		Not reported	4	21	7	17
Other						
23	Source of funding	Government	7	37	22	54
		Scientific association	1	5	0	0
		Industry	4	21	6	15
		Self-funded	0	0	3	7
		Not reported	7	37	10	24
24	Conflicts of interest	Conflicts of interest reported	9	47	6	15
		No conflicts of interest reported	6	32	13	32
		Not reported	4	21	22	54

(*Continues*)

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Table III. (Continued)

No.	Item	Value	TAVI (*N*)	TAVI (%)	ICD (*N*)	ICD (%)
Medical devices' distinctive features						
25	Learning curve	Formal	5	26	0	0
		Substantial	3	16	0	0
		Not considered	11	58	41	100
26	Incremental innovation	Formal	6	32	10	24
		Substantial	1	5	14	34
		Not considered	12	63	17	41
27	Dynamic pricing	Formal	2	11	9	22
		Substantial	9	47	13	32
		Not considered	8	42	19	46
28	Organisational impact	Formal	6	32	1	2
		Substantial	0	0	0	0
		Not considered	13	68	40	98

AVR, aortic valve replacement; ICD, implantable cardioverter defibrillator; ICER, incremental cost-effectiveness ratio; LYG, life year gained; MM, medical management; NHS, National Health Service; OMT, optimal medical therapy; QALY, quality-adjusted life year; RCT, randomised controlled trial; TAVI, transcatheter aortic valve implantation; WTP, willingness to pay.

Heterogeneity in subgroups of patients' parameters was investigated and reported for ICDs much more frequently than for TAVI (51% vs 5%). Study limitations are generally discussed (79% of studies for TAVI and 83% for ICDs). Funding source was reported for 63% of studies on TAVI and 76% on ICDs. In both cases, the studies were mainly either government (37% and 54% for TAVI and ICDs, respectively) or industry funded (21% and 15% for TAVI and ICDs, respectively). Authors' conflict of interest was acknowledged in 47% of EEs on TAVI and 15% on ICDs.

Overall, the methods applied in the studies of the two technologies were fairly representative of the wider literature on the EE of health technologies.

All the EEs on ICDs were very precise in reporting values, ranges and references of study parameters, while for TAVI only 65% did so. The summary measure of findings used as a decision criterion in the retrieved full EEs (for TAVI $n = 17$ and for ICDs $n = 40$) was the ICER, defined as the ratio of the differences in costs between treatments to the differences in effects between the same treatments. The ICER was always computed and explicitly reported, with the exception of Mabin and Candolfi (2014) who did not calculate the ICER but nonetheless concluded that TAVI is likely to be cost-effective.

Once calculated, the analysts compared the ICERs with threshold values, representing the maximum that society is willing to pay for an additional unit of health gain, in 84% of the economic analyses on TAVI and 45% on ICDs. It is worth noting that, among the countries represented in our sample, only the UK has an explicit ICER threshold, ranging between £20 000 and £30 000 (NICE, 2004). However, even though in most countries decision-making authorities have not defined an explicit ICER threshold, informal benchmarks are often used. In the Belgian HTA reports, the NICE threshold was used for comparison (Van Brabandt *et al*., 2006; Neyt *et al*., 2011). In the USA, no explicit cost-effectiveness threshold exists for the approval of new health technologies (Reynolds *et al*., 2012a, 2012b), but all the American EEs on TAVI referred to $US50 000/QALY as the cost-effectiveness threshold value (Gada *et al*., 2012a, 2012b; Reynolds *et al*., 2012a, 2012b). The same value was used by the Brazilian Secretary of Healthcare (Queiroga *et al*., 2013). All the Canadian studies referred to a willingness-to-pay threshold of $C50 000/QALY (Doble *et al*., 2013; Hancock-Howard *et al*., 2013), although interventions in the range of $C20 000–$C100 000/QALY were generally considered to provide reasonable value for money (Hancock-Howard *et al*., 2013).

Concerning the final recommendations, we distinguished between policy recommendations (i.e. set by HTA agencies) and journal articles' technical conclusions. While the latter normally conclude with a 'cost-effective/not cost-effective' result, the former are expected to provide an indication on adoption or rejection of the technologies. For both the technologies considered, we found that all studies classified them as either cost-effective or not cost-effective. However, in only a few cases did an HTA body exploit these results by recommending/not

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recommending adoption of the technologies in practice. For example, the Belgian Authority clearly denied the reimbursement of TAVI as a replacement for surgical treatment (Neyt *et al*., 2011) and the Australian Medical Services Advisory Committee declared the use of ICDs beneficial and appropriate only for selected categories of patients (Medical Advisory Secretariat, 2005). One study on ICDs did not reach any conclusive recommendation because of inadequacy of available evidence (McGregor and Chen, 2003).

3.3. Distinctive features of medical devices

The general level of awareness of the special characteristics of MDs appears to be low, considering the small number of studies citing them. Learning curve was mentioned in 42% of studies on TAVI. The analysts highlighted that, given the technology's innovative nature, operators' experience may affect outcomes (e.g. mortality, complication rates and quality of life) and efficiency (e.g. procedure duration and length of stay). However, this variable was considered in sensitivity analyses in only 16% of the studies, by varying the rate of complications and procedure success. For ICDs, a mature technology characterised mainly by incremental innovation, the operator's experience is not considered to be important and therefore none of the studies mentioned it.

Incremental innovation was more frequently mentioned in the studies of ICDs than in those of TAVI. Its impact was considered in sensitivity analysis in only 34% of ICD studies—where newer generations of devices with improved battery capacity and lower probability of implant failure were tested. The impact of incremental innovation was only considered in one TAVI study, where the impact of the technological refinements in the newer generations of valves was estimated by changing the rate of procedure-related events to reflect likely better performance.

Dynamic pricing was by far the most recognised feature and was empirically tested by varying the devices' price in 47% and 32% of studies on TAVI and ICDs, respectively.

Organisational impact was mentioned in only one ICD study. In the case of TAVI, it was cited by all HTA reports except for one, although none of them estimated its impact, while it was completely ignored in published EEs. In general, the HTA reports focused on four main aspects of potential organisational impact: hospitals' capital equipment (e.g. joint presence of cardiac and vascular surgical services, integrated cardiac surgery and interventional cardiology, and hybrid operating room), creation of multidisciplinary teams in charge of selecting and treating patients, minimum yearly volume of procedures per centre to ensure safety of implantations (as defined by scientific associations), and operators' need for supervision.

4. DISCUSSION

The aim of this study was to gather evidence on how MDs are currently assessed in practice and to identify any recurring methodological deficiencies. This analysis is instrumental to the ultimate goal of MedtecHTA project, that is to provide recommendations on how to improve the assessment of MDs, as reported in this supplement by Tarricone *et al*. (2017). Therefore, we adapted the CHEERS checklist to assess EE analyses of MDs and applied this in two case studies: TAVI, a recently introduced device, and ICDs, a mature technology. A systematic literature review was conducted to retrieve relevant studies. A total of 19 studies for TAVI and 41 studies for ICDs were finally included in the analysis. This is the most complete and comprehensive review undertaken to date, as it included all documents in any language made available without any time limit.

For the emerging technology, TAVI, economic evidence was considered in studies only 5 years after the technology's introduction in the market, when already more than 34 000 implants had been performed in Europe (Mylotte *et al*., 2013). The first HTA reports appeared 1 year after CE marking but were based on clinical aspects (e.g. case series, case studies and manufacturers' reports) and provided indications on safety and efficacy only. This finding clearly illustrates some of the typical challenges of assessing MDs, such as the lack of evidence at the time of market approval and the relevance of collecting post-marketing evidence, accompanied by an iterative process to assess the new evidence as it is generated (Drummond

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et al., 2009; Tarricone *et al*., 2014; Ciani *et al*., 2017). Interestingly, although the lack of evidence leads to difficulties in conducting full HTAs, this does not seem to have delayed the uptake of TAVI in Europe, where the yearly implant rate grew by 815% in the first 5 years, that is before its use in any indication was formally recommended by HTA agencies. Uptake and diffusion of innovative devices often goes beyond evidential requirements and also depends upon end users' beliefs and opinions, as investigated by Hatz *et al*. (2017) within the MedtecHTA project. This suggests the need for a controlled diffusion of the technology aimed at collecting post-marketing evidence to support decision-makers in reviewing their recommendations, at least until the point where the device has reached a steady state and/or has become obsolete.

The methods used to conduct EE analysis of TAVI and ICDs were similar between HTA reports and journal articles. We found some differences in the types of sources used in the case of ICDs only, where EEs conducted by HTA agencies used RCTs as the exclusive source of clinical evidence and were mostly model based; that is, longer time horizons were considered than EEs published in journal articles.

Independently from who conducted the economic analysis of TAVI and ICDs, we found differences in terms of perspective and time horizon. National health service and third-party payer were the most frequently adopted perspectives, even when non-HTA agencies were the evaluators. Although there were studies that claimed to adopt the societal perspective, this was not consistent with the actual inclusion of cost components, given that almost all studies took into account only direct healthcare costs and ignored other categories such as productivity losses and informal care that—for instance—might have been relevant for the evaluations of ICDs and TAVI. As to time horizon, we found that it greatly impacted the results of the ICD studies. The longer the time used in the EEs, the higher the probability of finding the technology to be cost-effective. These findings pose the issues of (i) consistency between the perspectives adopted and the cost components considered in the analysis and (ii) the appropriateness of time horizon, which has to be defined consistently with patients' life expectancy, the device's longevity and its estimated substitution rate.

Consistent with the findings by Ciani *et al*. (2017), RW data were used less frequently than RCTs as sources of clinical evidence. This holds true for both categories of device studied, although RW data were available in both cases before the economic analyses were published. RW data play an important role in the assessment of MDs and need to be either correctly integrated into evidence synthesis of clinical and economic data when available (e.g. meta-analysis and network meta-analysis) or appropriately analysed so as to adjust for biases such as selection bias. Several methods can be used to accomplish this, such as expert elicitation (Schnell-Inderst *et al*., 2017), multivariate regression or non-parametric techniques based on the propensity score and, in particular, matching techniques (Tarricone *et al*., 2017).

The specific characteristics of MDs, such as learning curves, incremental innovation, dynamic pricing and organisational aspects, were mentioned—although not frequently—in the retrieved studies, but their impact was rarely measured. This finding, based on more detailed research, is consistent with the findings by Ciani *et al*. (2017) and points to the general issues of limited evidence availability when the initial adoption decision has to be taken and, more importantly, to the difficulty in estimating the quantitative impact of these characteristics on cost-effectiveness. It is therefore unclear whether the findings of the studies would have substantially changed had these aspects been estimated.

For instance, the learning curve effect for TAVI was assessed in three studies (Calcerrada *et al*., 2010; Murphy *et al*., 2013; Orlando *et al*., 2013), and its impact was mainly measured in terms of improvements in procedure-related events, that is a reduction of resource consumption. It is more difficult to estimate the impact of the learning curve effect on patient outcomes. This was performed in the MedtecHTA project, where a moderate, but significant, effect of learning on both in-hospital mortality and hospital length of stay was estimated for endovascular aneurysm repair (Varabyova *et al*., 2017). To empirically estimate the learning curve effect, it is important to measure the number of procedures needed to reach the flat of the curve, as calculating the ICER before or after that number is not trivial for decision-making. Once the device has entered the market, RW data would need to be collected at the patient, end user and hospital levels, aimed at measuring the impact of the learning curve on the incremental cost-effectiveness ratio and to determine the key drivers of those effects (e.g. volume of procedures by clinician, frequency of procedures and hospital specialisation). In the case

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of TAVI, the cumulative number of procedures per medical staff (or hospital) could have been correlated to health outcomes such as survival or quality of life, or—at least—to outputs such as procedural success, length of stay and time in intensive care units, which are usually considered good predictors of clinical effectiveness and economic efficiency. This was performed in the EE of Mitraclip®, a cardiac device with similar characteristics to TAVI (Armeni *et al*., 2016).

Incremental innovation normally refers to product modifications aimed at easing the delivery of the procedure (e.g. making the procedure less complicated) and/or increasing its performance in terms of health outcomes. MDs such as ICDs are often subject to incremental innovations. Because incremental innovation is often facilitated by the interaction between manufacturers and end users, it is a continuous process, which makes it difficult to forecast when the 'increments' would actually accrue and, more importantly, whether and how these modifications would have a concrete impact on the costs and/or effectiveness of the technology/procedure, so as to lead decision-makers adopt the newer version of the device. As stated by Rothery *et al*. (2017) in this supplement, an iterative Bayesian approach could be used to address the question of the 'optimal' timing of adoption or reimbursement decisions. Preliminary recommendations can be restrictive while waiting for further evidence to confirm the initial hypotheses. Also in this case, post-market RW data can be of help and, for some devices, represent the only realistic option. Because incremental innovations often refer to small but continuous product changes, it is difficult to conduct RCTs for every single product development. RW data collected while the device moves along its life cycle curve would help in adjusting initial assumptions and help formulate more conclusive recommendations. ICDs are a good example of incremental innovations. Today their size is less than a €2 coin, with batteries that last longer than 5 years. This evolutionary process started more than 50 years ago and still continues ceaselessly. Clinical evidence is regularly produced, although often not in the form of controlled studies. Economic modelling can be of help in these cases; that is, it helps in synthetising available evidence to predict future device performance, health outcomes and procedural costs.

Pricing of MDs is more dynamic than that of drugs because of different regulation and procurement policies. Prices of new devices often influence the prices of existing devices, as in the case of drug-eluting stents (Drummond *et al*., 2009). These considerations raise the level of uncertainty concerning when a new device must be assessed to decide about its introduction and reimbursement. Dynamic pricing was by far the most recognised characteristic in our literature review on TAVI and ICDs but was empirically tested in less than half of the studies. For the healthcare system, the optimal price for a new technology is the one that—other conditions being equal—describes the threshold price at the point of indifference between accepting and rejecting the technology (Rothery *et al*., 2017). The case study of enhanced external counterpulsation, discussed in this supplement by Rothery *et al*., exemplifies how uncertainty can determine different value-based prices, each of which represents the threshold price at which the decision option changes (e.g. approval with research vs only in research and approve vs approval with research). The same approach could be adopted for TAVI and ICDs by using current prices to measure the value of health outcomes forgone so to determine whether they are worth paying or, conversely, what would be the value-based price that is justified by the added clinical benefits. Determining the value-based price that would change the recommendation would also incentivise the collection of additional, RW post-market clinical and economic evidence, aimed at verifying the model assumptions such as the expected changes of prices of competitors.

Finally, the organisational impact differs from the previous three characteristics because it mainly refers to the impact of the introduction of new devices at the hospital or provider level and may not greatly affect the decision on reimbursement that is generally taken at a central level. However, MDs, more often than drugs, may need *ad hoc* training or capital equipment to be appropriately delivered. Some of these costs can be irrecoverable and would need to be considered in the cost-effectiveness analysis/HTA modelling in order to find out how long it would take to break even. The approach suggested by Rothery *et al*. (2017) for enhanced external counterpulsation in this supplement could also apply to TAVI procedures, which would require hospitals to incur initial capital equipment costs for hybrid rooms. This is also why time horizon is an important issue for the assessment of those MDs that require large upfront investment costs and several years to show

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the incremental benefits, as we found in our literature review of ICDs. The issue is that while initial costs are known and can be imputed in the preliminary model, actual benefits are uncertain and can be observed only over time, through follow-up studies. This is another reason in favour of an iterative assessment process for MDs that should make use of clinical evidence—especially RW data—as it accumulates over time.

This study has some limitations. We have focused our analyses on cardiac devices only, and our findings and conclusions must be viewed with caution when other sectors are considered. Moreover, we have investigated two devices only, and although we differentiated between recently introduced and mature technologies, further research would be needed to assess the generalisability of our findings to other types of MDs.

Finally, with this study, we have shown that there is a *prima facie* case for considering the particular characteristics of MDs, and our findings suggest that in the main these characteristics are not adequately considered. Further research would need to be conducted into whether the failure to give adequate consideration to these features greatly impacts the estimation of cost-effectiveness.

5. CONCLUSIONS AND RECOMMENDATIONS

Our analysis identifies where and how the assessment of MDs can be improved, by changing current methods to evaluate the technologies and helping policymakers become more confident in providing recommendations. These changes mainly relate to the distinctive characteristics of MDs, that is learning curve effect, dynamic pricing, incremental innovation and organisational impact. All these characteristics can heavily impact the cost-effectiveness ratio of devices and therefore need to be quantitatively assessed. But they also increase the level of uncertainty, especially at uptake when policymakers are expected to make preliminary recommendations on whether and how the new device can be used in regular practice. This can be carried out by estimating their effect through appropriate and sophisticated modelling aimed at calculating the impact of the most relevant characteristics based upon clinical and economic data to be developed according to an agreed research protocol between the regulators, policymakers and device manufacturers (e.g. based on early dialogue). The result of this process, often called ‘coverage with evidence development’, may often be a non-definitive recommendation, for example adoption only in research or approval within research. Before the device becomes adopted in routine practice, further assessment would need to confirm the assumptions of previous modelling efforts and would ideally rely upon post-market clinical and economic evidence collected in a limited number of providers. Well-developed post-market study protocols and appropriate techniques for bias adjustments would help reduce the level of uncertainty and make policymakers more confident to formulate a definite recommendation on the reimbursement and use of the device.

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