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LINKING THE REGULATORY AND REIMBURSEMENT PROCESSES FOR MEDICAL DEVICES: THE NEED FOR INTEGRATED ASSESSMENTS

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ABSTRACT

Much criticism has been directed at the licencing requirements for medical devices (MDs) as they often result in a lack of robust evidence to inform health technology assessment (HTA) decisions. To better understand the current international decisional framework on MD technologies, we undertook three linked research studies: a review of the device regulatory procedures, a survey of current HTA practices and an empirical comparison of HTA reports of drugs versus MDs. Our review confirms that current device regulatory processes across the globe are substantially less stringent than drugs. As a result, international HTA agencies report that they face a number of challenges when assessing MDs, including reliance on suboptimal data to make clinical and cost-effectiveness decisions. Whilst many HTA agencies have adapted their processes and procedures to handle MD technology submissions, in our comparison of HTA reports we found little evidence of the application of methodologies that take account of device-specific issues, such as incremental development. Overall, our research reinforces the need for better linkage between licencing and HTA and the development and application of innovative HTA methodologies with the objective of securing faster patient access for those technologies that can be shown to represent good value for money. © 2017 The Authors. *Health Economics* Published by John Wiley & Sons, Ltd.

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1. INTRODUCTION

Health technology assessment (HTA) seeks to synthesise information on the clinical, economic, social and ethical value of health technologies, including pharmaceuticals, medical devices (MDs), clinical procedures and organisational systems, used in healthcare, with the aim of informing the formulation of safe and effective health policies, particularly in relation to reimbursement or coverage decisions (Banta, 2009). However, HTA and economic evaluation methods have been largely developed with the evaluation of drugs or pharmaceuticals in mind (Franken *et al*., 2012; Oortwijn *et al*., 2010). As a consequence, a number of commentators have argued the generic application of international HTA methods guidelines to non-drug technologies, especially MDs, to be inappropriate, and that these methods overlook important differences between drug and devices (Drummond *et al*., 2009; Kirisits and Redekop, 2013; Sorenson and Drummond, 2014; Taylor and Iglesias, 2009). In brief, these differences can be broadly characterised under three headings: (i) *nature of the* (*clinical*) *evidence base*: traditionally lower licencing of requirements for devices than drugs has meant that the clinical

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evidence base for a device may consist of data that are prone to the problems of selection bias and confounding, with little or no randomised controlled trial (RCT); (ii) *nature of the device technology*: unlike drugs, devices often undergo incremental evolution over time that can rapidly change the technology under assessment. Furthermore, as they typically are only one component of a clinical procedure, patient-related outcomes often depend on training and experience of the operator together with the setting in which the device is applied; and (iii) *pricing*: MDs pricing is more dynamic compared with drugs because of the market entry of new device products or because of the ways in which procurement takes place in many healthcare systems. Technology manufacturers and policymakers are placing increased pressure on the HTA and health economics communities to develop their current assessment methods to better take account of these features of MDs (Ferrusi *et al*., 2009). For example, in recognition of the challenges faced by industry, as well as the growing need for cost-effective allocation of National Health Service resources, the National Institute for Health and Care Excellence (NICE) in England and Wales led the development of the Medical Technologies Evaluation Programme (MTEP), which launched in 2009/2010. However, an analysis of the output of MTEP's first 3 years suggests that it has some way to go to meet pre-specified aims of simplifying access to evaluation, speeding up the process and increasing evaluative capacity for devices within NICE (Chapman *et al*., 2014).

In response to this background, in 2013 the European Commission under its seventh Framework Programme funded the 'Methods for Health Technology Assessment of Medical Technologies (MedTecHTA)' project with the overarching aim of improving the existing HTA and economic evaluation methodological framework for the assessment of MDs (Università Bocconi - CERGAS, 2016). A starting point for the MedTecHTA project was to review current approaches and methods for the evaluation of MDs under the first of the seven work packages included in the overall research programme. Three linked research studies were designed: a review of the international regulatory procedures for devices, a survey of current international HTA practices for devices and an empirical comparison of the application of methods in HTA reports of drugs versus devices. Given the details of the first two studies having been published elsewhere (Ciani *et al*., 2015; Tarricone *et al*., 2014), here we focus on the third project. The remainder of the paper provides a brief synopsis of the previous research performed, illustrates the methods and results of the HTA report comparative study and closes with a discussion that jointly considers the implications of the findings of work package 1. The overarching aims are to provide a contemporary review and critique of existing regulatory and HTA approaches for MDs and to make informed recommendations to improve the policy evaluative framework for these technologies.

1.1. Current international regulatory and health technology assessment practices for medical devices

In 2014, Tarricone *et al*. (2014) investigated current regulatory practices for MDs based on a systematic review of the literature and on interviews with regulatory agencies across a number of international jurisdictions, including the EU (European Commission Directorate-General for Health and Consumers, Health Technology and Cosmetics unit), the USA (Food and Drug Administration, FDA), Australia (Therapeutic Goods Administration), Canada (Health Canada) and China (China Food and Drug Administration). The review shed light on several issues. First, the framework for device regulation is complex, in no small part because of the great diversity of technologies. Second, existing regulatory processes for MDs generate less clinical evidence than the corresponding processes for drugs. Third, MDs are assigned to one of several regulatory classes, generally based on the risk associated with the device, the manufacturers' intended purpose for the device and the device's indication for use. In the EU, the European Commission Medical Devices Directive 93/42/EEC defines four categories of devices, graded according to the risk assessment, considering the following four dimensions: (i) duration of contact with the patient; (ii) the invasiveness; (iii) the intended use and dependence on an external source of energy; and (iv) the location of the anatomical area affected. The device class determines, among other things, the level of evidence and evaluation required to demonstrate safety and efficacy (e.g. invasive and high-risk devices require more evidence); however, there are substantial differences in these requirements across jurisdictions. In particular, and in contrast to the USA, the current system of regulation in EU typically does not require adequately powered RCTs for the approval of a high-risk device. Fourth, a common approach

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employed to speed up the regulatory process is to allow new devices to claim similarity to other devices already on the market (e.g. the 510(k) process of the US FDA). The US Supreme Court has acknowledged that substantial equivalence is no guarantee that an MD is safe and effective, and previous authors have suggested that if some of the 510(k)-cleared devices had been subject to a full pre-market application process, their risks may have been identified sooner (Campillo-Artero, 2013). Finally, although regulatory processes consistently impose obligations on the manufacturer for post-market surveillance, such post-approval monitoring approaches are often limited to passive reporting of adverse events for marketed devices.

After better understanding the complexities of MD regulation, we sought to investigate how HTA agencies evaluate these technologies in the context of recommendations or decisions on their coverage, reimbursement or use. To meet this aim, Ciani *et al*. (2015) surveyed the activities for MDs across 36 non-EU HTA agencies. Data collection was performed in two stages – an agency website assessment using a standardised questionnaire followed by a semi-structured telephone interview with agency personnel in a subsample of organisations. The survey had three principle findings. First, although 27 (75%) of the agencies surveyed had adopted HTA-specific approaches for devices, these were largely organisational (e.g. allocation of specific staff to MDs assessment) or procedural (e.g. convening a specific committee to appraise device evidence and provide policy advice) in nature. The heterogeneity of agency procedures is an important challenge to manufacturers who want to embark in the HTA process across several jurisdictions. Second, only one agency (i.e. Department of Science and Technology in Brazil) had developed methodological guidelines specific to MDs (Ministry of Health of Brazil, 2014). Finally, in addition to the problem of lack of robust clinical evidence, many interviewed agencies cited insufficient resources (e.g. budget and skilled employees), lack of coordination between regulatory and reimbursement bodies, and the inability to generalise findings from evidence syntheses, to be key challenges in the HTA of devices.

1.2. Comparative assessment of health technology assessment reports on medical devices and drugs

Although limitations of currently available methods for HTA and economic evaluation with respect to MDs have been highlighted in the scientific literature (Cohen and Billingsley, 2011; Kramer *et al*., 2012; Sorenson and Drummond, 2014), no formal comparison of the application of such methods in HTA reports of MDs versus a comparable sample of HTA reports of drug technologies has been reported. This third study in work package 1 sought to address the following specific research questions: (i) What is the nature of evidence and outcomes included in the HTA reports on MDs compared to drugs? (ii) Do the methods (e.g. systematic review and economic evaluation) applied in HTA reports on MDs and drugs differ? and (iii) How data uncertainty is addressed and reflected in the technology adoption or policy recommendation in the HTA reports on MDs compared to drugs? Given that cardiovascular is the second largest device sector, following *in vitro* diagnostics, in terms of sales, sales growth and market share worldwide (MedTech Europe, 2015), and because we could capitalise on the partnership with the European Society of Cardiology within the MedTecHTA project, it was decided to focus this comparison of devices and drugs HTA reports to the field of cardiovascular disease.

2. METHODS

2.1. Identification of health technology assessment reports

Health technology assessment reports were identified by searching the University of York Centre for Reviews and Dissemination HTA database from 2003 to 2014. The search strategy is listed in Appendix A.

2.2. Selection and screening of reports

We included HTA reports if they assessed a drug or device where the primary indication was cardiovascular disease (i.e. cerebrovascular, cardiac or peripheral vascular disease). We excluded reports that had a primary

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indication that was not cardiovascular disease; assessed surgical procedures without an MD; addressed a diagnosis or prognosis question; were mainly guidelines or overviews that assessed the management of disease indication rather than specific technologies; were not full HTA reports (i.e. a comprehensive systematic assessment of new or established health technologies that evaluates several dimensions including effect, safety and cost-effectiveness and often issues relating to ethical, legal, organisational and social consequences; Velasco *et al*., 2002); and were not publically available as full text in English. Two members of the research team (B. W. and R. S. T.) independently screened all titles and abstracts for inclusion. Where there were disagreements about the inclusion of reports, these were discussed and consensus was reached.

2.3. Data extraction and quality assessment

Using a standardised data extraction tool, we sought the following categories of information from the included HTA reports: general information (e.g. study title, name of agency publishing HTA report), nature of evidence (e.g. type of clinical or economic studies included), methods applied (e.g. systematic review and economic evaluation), results (e.g. treatment effect for the all-cause mortality outcome), technology-specific considerations (e.g. incremental innovation of a device or mode of drug administration), methods for handling uncertainty (e.g. sensitivity analysis) and conclusions (e.g. final policy recommendation).

The nature of the primary outcome(s) presented in drug and device reports were categorised as 'final' or 'surrogate', according to a common definition whereby a surrogate is a biomarker or intermediate outcome intended to substitute for a patient-relevant outcome (Biomarkers Definitions Working Group, 2001). We applied this classification to the primary outcomes in each HTA report (i.e. the stated primary outcome of report or, where not stated, the first outcome discussed in the report). Because cardiovascular disease is a leading cause of death, we sought to extract the reported treatment effects for both all-cause mortality and, where stated, the primary outcome. The base case incremental cost-effectiveness ratio was also recorded. The policy recommendations of reports were categorised according to the National Institute for NICE technology appraisal outcomes (NICE, 2013): (i) *recommended*: approved for use of an intervention throughout health system, for either all or specific licenced indications or patient subgroups; (ii) *optimised*: approved for routine use of specific licenced indications or patient subgroups; (iii) *only in research*: use of the intervention only in the context of appropriate research; (iv) *not recommended*: denied approval due to inadequate evidence of clinical or cost-effectiveness.

We assessed the methods used by HTA reports based on two dimensions of quality: Systematic review methods were assessed using the Measurement Tool to Assess Systematic Reviews (AMSTAR) (Shea *et al*., 2007; Shea *et al*., 2009), and economic evaluation methods were assessed using a validated checklist (Drummond *et al*., 2005). An AMSTAR score is calculated by summing the individual items with a maximum score of 11 for quality. We used the 10-point Drummond checklist to assess the validity of economic evaluations presented in the included HTA reports. A set of previously described global weighted values associated with the Drummond checklist items were applied in this study (Drummond and Jefferson, 1996; La Torre *et al*., 2010). Where multiple questions from the 35-point checklist related to a single question on the 10-point checklist, a new weight was calculated by averaging the global weights of the related questions. The maximum possible economic evaluation quality score was 43.3. The initial list of data extraction items was piloted on a drug HTA report selected at random. Following this pilot application, we modified items and, where necessary, updated them with corresponding instructions. The items were further tested on one randomly selected device report. The final 67 data extraction items are listed in Appendix B. Data from all included HTA reports were extracted by one member of the research team (B. W.) and independently checked by a second reviewer (A. G.).

2.4. Data analysis

Quantitative data (e.g. number of RCTs included in a report) were summarised across reports using medians, ranges and percentages. We compared the summary results between MDs and drug HTA reports using non-parametric statistics (i.e. Mann–Whitney test for continuous and categorical outcomes and Fisher's exact or

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chi-squared tests for binary outcomes). We sought to compare the size of treatment effects of devices and drugs by using meta-analyses to pool report mortality and, where stated, primary outcome results. This comparison would reveal whether specific methodological adjustments would be justified by, on average, significantly different treatment effects produced by device technologies rather than drug technologies in the cardiovascular field. Descriptive information (e.g. methods of handling uncertainty) was thematically analysed and, where possible, compared across device and drug reports.

Data were initially extracted into an MS Office Access form, and quantitative and qualitative data were analysed using STATA© 13.2 StataCorp LP.

3. RESULTS

3.1. Description of included health technology assessment reports

The HTA report selection process is summarised in Figure 1. Out of the 699 HTA reports screened, 45 HTA reports met the inclusion criteria and were included in the review (Table I). Of these, 18 were MD reports and 27 were drug reports and were predominantly from Canada ($n = 15$), the UK ($n = 20$) and the USA ($n = 8$). The included MD and drug reports were broadly similar in terms of their publication date, cardiovascular indication and issuing agency. All reports considered 'medium-risk' or 'high-risk' (i.e. class IIa or above) devices according to the European Commission Medical Device classification system (Council of the European Communities, 1993).

3.2. Nature of evidence and outcomes

Device reports were more likely to include non-RCT/observational studies than drug reports (44%/48% vs 22%/17%) (Table II). When drug or device reports did consider RCTs, they included a similar number of RCTs (median of five RCTs per report). However, the average number of patients in RCTs, non-RCTs and observational studies included in drug reports were threefold larger than in MD reports. The majority of both drug

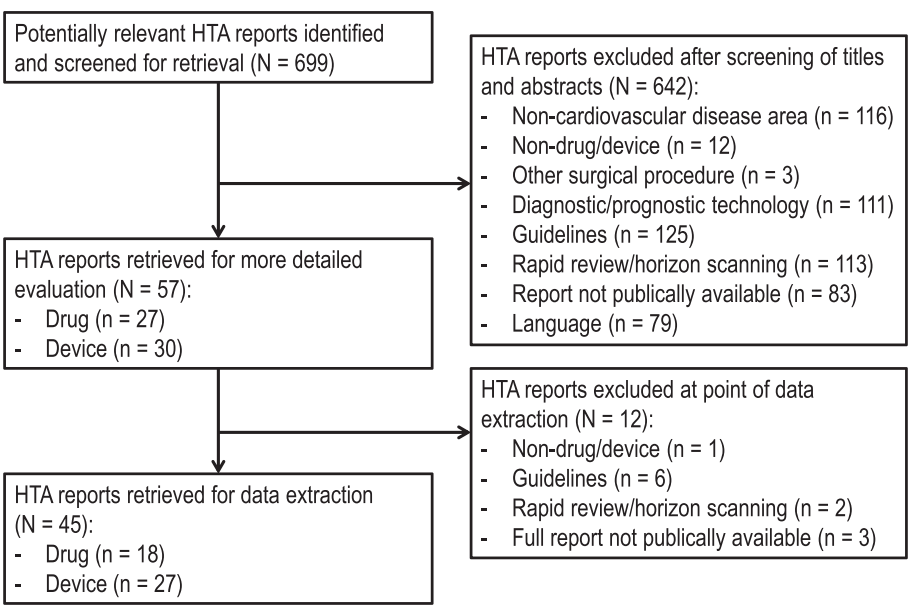

Figure 1. Summary of the process of selection of health technology assessment (HTA) reports

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Table I. Summary of key characteristics of included health technology assessment reports

	Drug ($N = 18$)	Device ($N = 27$)	Drug versus device
	n (%)	*n* (%)	*P*-value
Publication date			
2003–2008	2 (11)	2 (7)	1.00[a]
2009–2013	16 (89)	25 (93)	
Country of publication			
Australia	0 (0)	1 (4)	0.13[b]
Canada	3 (17)	12 (44)	
Republic of Ireland	0 (0)	1 (4)	
United Kingdom	12 (67)	8 (30)	
United States	3 (17)	5 (19)	
Cardiovascular indication			
Cerebrovascular	2 (11)	0 (0)	0.20[b]
Cardiac	12 (67)	19 (70)	
Peripheral	4 (22)	8 (30)	
Device class			
Class I (low risk)	NA	0 (0)	—
Class IIa (medium risk)	NA	3 (11)	
Class IIb (medium risk)	NA	5 (19)	
Class III (high risk)	NA	19 (70)	

NA, not applicable.
[a]Fisher's exact test.
[b]Chi-squared test.

Table II. Nature of evidence considered by health technology assessment reports

	Drug ($N = 18$)		Device ($N = 27$)		Drug versus device	
	n (%)	Median (range)	*n* (%)	Median (range)	*P*-value for %[b]	*P*-value for median[a]
Type of clinical study						
RCTs	17 (94)	5 (1; 35)	18 (67)	5 (1; 82)	0.03	0.92
Non-RCTs	4 (22)	5.5 (1; 18)	12 (44)	6 (2; 29)	0.13	0.43
Observational studies	3 (17)	46 (13; 92)	13 (48)	25 (4; 53)	0.03	0.24
Evidence synthesis[c]	6 (33)	5.5 (5; 30)	8 (30)	5 (1; 15)	0.79	0.30
Other[d]	1 (6)	89 (NA)	2 (7)	1.5 (1; 2)	0.81	0.22
Number of patients						
RCTs	13 (72)	4203 (34; 66 477)	12 (44)	1482 (291; 35 597)	—	0.23
Non-RCTs	3 (17)	4917 (926; 184 372)	5 (19)	836 (79; 12 217)	—	0.18
Observational studies	1 (6)	7636 (NA)	7 (26)	646 (76; 13 890)	—	0.51
Evidence synthesis[c]	1 (6)	102 594 (NA)	1 (4)	102 594 (NA)	—	0.32
Type of economic evaluation						
Cost analysis	1 (6)	5 (NA)	4 (15)	1.5 (1;2)	0.33	0.14
Cost minimisation analysis	0 (0)	—	0 (0)	—	—	—
Cost-effectiveness analysis	8 (44)	4 (1; 20)	9 (33)	2 (1; 8)	0.45	0.53
Cost–utility analysis	8 (44)	3.5 (1; 8)	9 (33)	1 (1; 4)	0.45	0.11
Cost–benefit analysis	0 (0)	—	1 (4)	1	0.41	—
Cost–consequence analysis	0 (0)x	—	0 (0)	—	—	—

RCTs, randomised controlled trial; HTA, health technology assessment.
[a]Mann–Whitney test.
[b]Fisher's exact test.
[c]Systematic reviews, meta-analyses and HTA reports.
[d]Rapid reviews and sources of evidence that do not fall into the aforementioned hierarchy of evidence categories.

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reports (17/18, 94%) and device reports (23/27, 85%) examined economic studies in the form of either partial or full evaluations.

Following the HTA Core Model® classification (EUnetHTA Joint Action 2 Work Package 8, 2016), both drug and MD reports consistently consider safety, effectiveness and economic evidence (Table III). Device reports were less likely than drug reports to provide a detailed description of the technology and associated disease indication. Conversely, 44% (12/27) of MD reports, compared with 6% (1/18) of drug reports, considered organisational issues. Thirty-six of the 45 reports (82%) considered final outcomes (e.g. all-cause mortality and cardiovascular mortality), 14/18 (78%) and 22/27 (81%) for drug and MD reports, respectively. The remaining nine reports considered surrogate outcomes (e.g. Low density lipoprotein (LDL)-cholesterol, maximal walking distance and mean time to conversion from atrial fibrillation to normal sinus rhythm); five (19%) of these reports were device reports, and four (22%) were drug reports.

3.3. Data synthesis methods applied by health technology assessment reports

The majority of drug and MD reports included a systematic review of both clinical (37/45, 82%) and economic studies (19/45, 42%) (Table IV). Drug reports were more likely than MD reports to undertake a meta-analysis (10/18, 56% vs 9/27, 33%). About 60% of drug and device reports undertook a *de novo* model-based economic analysis. The quality of both systematic reviews and economic evaluation methods appeared to be higher for drug reports than for MD reports. The mean AMSTAR score for drug and device reports was 7.5 and 5.5, respectively (maximum possible score is 11). For the Drummond checklist, the mean score for drug and device reports was 29 and 21, respectively (maximum possible score is 43.3).

The majority of drug (16/18, 89%) and MD (18/27, 67%) reports included consideration of technology-specific issues. For drugs, dosage, duration of treatment and mode of administration were all commonly reported. For MDs, the most common issues were healthcare setting of use, learning curve and the device generation or model. However, these technology-specific issues were typically limited to a brief mention in the discussion of the HTA report. None of the reports included a formal quantitative analyses to assess how these issues may impact the clinical or cost-effectiveness of the device.

About 60% of drug and MD reports undertook uncertainty evaluation in their clinical and economic effectiveness sections. For both, the most commonly considered methods were sensitivity analyses, either deterministic or probabilistic; use of 95% confidence intervals; and reporting of *P*-values.

3.4. Size of treatment effects and economic outcomes

We sought to compare drug and MD reports based on pooling across reports the clinical treatment effect on all-cause mortality and incremental cost-effectiveness ratio. However, the types of clinical and economic outcomes

Table III. EUnetHTA HTA core model® dimensions in HTA reports

	Drug ($N = 18$)	Device ($N = 27$)	Drug versus device
	n (%)	*n* (%)	*P*-value[a]
Health problem and current use of technology	15 (83)	10 (37)	<0.001
Description and technical characteristics of technology	15 (83)	8 (30)	<0.001
Safety	12 (67)	17 (63)	0.80
Clinical effectiveness	17 (94)	24 (89)	0.64
Cost and economic evaluation[b]	13 (72)	20 (74)	1.00
Ethical aspects	1 (6)	1 (4)	1.00
Organisational aspects	1 (6)	12 (44)	<0.001
Social aspects	5 (28)	3 (11)	0.24
Legal aspects	1 (6)	1 (4)	1.00

[a]Fisher's exact test.
[b]Count includes a report if it included a systematic review of economic analyses or *de novo* economic model.

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Table IV. Evidence synthesis methods of HTA reports

Method	Drug ($N=18$) Total N	Drug ($N=18$) *n* (%)	Device ($N=27$) Total *N*	Device ($N=27$) *n* (%)	Drug versus Device *P*-value [a]
Methods of data synthesis					
Systematic review of clinical outcomes	18	14 (78)	27	23 (85)	0.52
Meta-analysis	18	10 (56)	27	9 (33)	0.14
Systematic review of economic evaluations	18	9 (50)	27	10 (37)	0.39
Economic model	18	11 (61)	27	17 (63)	0.90
AMSTAR (systematic review quality)					
Was an '*a priori*' design provided?	15	13 (87)	24	12 (50)	0.04
Was there duplicate study selection and data extraction?	15	13 (87)	24	10 (42)	0.01
Was a comprehensive literature search performed?	15	14 (93)	24	20 (83)	0.78
Was the status of publication (i.e. grey literature) used as an inclusion criterion?	15	10 (67)	24	18 (75)	0.65
Was a list of studies (included and excluded) provided?	15	12 (80)	24	8 (33)	<0.001
Were the characteristics of the included studies provided?	15	10 (67)	24	20 (83)	0.36
Was the scientific quality of the included studies assessed and documented?	15	14 (93)	24	17 (71)	0.078
Was the scientific quality of the included studies used appropriately in formulating conclusions?	15	10 (67)	24	13 (54)	0.32
Were the methods used to combine the findings of studies appropriate?	15	9 (60)	24	9 (38)	0.17
Was the likelihood of publication bias assessed?	15	6 (40)	24	3 (13)	0.12
Was the conflict of interest included?	15	1 (7)	24	2 (8)	1.00
Total score – mean (standard deviation)	15	7.5 (2.2)	24	5.5 (2.7)	0.04[b]
Drummond checklist (economic evaluation quality)					
Was a well-defined question posed?	11	4 (36)	17	8 (47)	0.71
Was a comprehensive description of the competing alternatives given? (i.e. can you tell who did what to whom, where and how often?)	11	11 (100)	17	11 (65)	0.06
Was the effectiveness of the programmes or services established?	11	7 (64)	17	8 (47)	0.46
Were all the important and relevant costs and consequences for each alternative identified?	11	7 (64)	17	10 (59)	1.00
Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost work-days and life-years gained)?	11	7 (64)	17	8 (47)	0.46
Were costs and consequences valued credibly?	11	10 (91)	17	12 (71)	0.36
Were costs and consequences adjusted for differential timing?	11	8 (73)	17	9 (53)	0.44
Was an incremental analysis of costs and consequences of alternatives performed?	11	11 (100)	17	9 (53)	0.01
Was allowance made for uncertainty in the estimates of costs and consequences?	11	10 (91)	17	10 (59)	0.10
Did the presentation and discussion of study results include all issues of concern to users?	11	8 (73)	17	10 (59)	0.69
Total Weighted Score – mean (standard deviation)	11	29 (7.1)	14	21 (9.2)	0.03[b]

HTA, health technology assessment; AMSTAR, Measurement Tool to Assess Systematic Reviews.
[a]*P*-value calculated using Fisher's exact test.
[b]*P*-value calculated using Mann–Whitney *U*-test.

presented across reports, outcome metrics (e.g. odds ratio and hazard ratio) and definition (e.g. all-cause mortality, cardiovascular mortality and vascular death) and point of follow-up (e.g. 7 days, 30 days and 6 months) were highly heterogeneous. Therefore, pooling of treatment effects across reports in this study was deemed inappropriate. A proportion of drug (4/18, 22%) and MD (7/27, 26%) reports included a pooled value for all-cause mortality based on a meta-analysis. Ten (56%) drug and 16 (59%) device reports presented a base case incremental cost-effectiveness ratio. There was no evidence of substantive difference in magnitude of mortality benefit or the cost-effectiveness ratio for the experimental technologies (compared with control) in MD reports compared with drug reports.

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3.5. Policy recommendations made by health technology assessment reports

Only a minority of reports (5/18, 28% drug, and 6/27, 22% MDs) included a policy recommendation (Table V). Where reported, there was no evidence of difference in the type of recommendation provided by authors of drug or MD reports. However, a higher proportion of MD reports (83% vs 21%) recommended 'optimised' adoption indicating that, probably because of pre-market evidence or evidence quality gaps or need to understand use in practice, for devices there is more room for streamlining the indications at the time of the assessment.

4. DISCUSSION

The development of new and innovative MDs plays a central role in the management of disease and promotion of health. In 2015, the global market was valued at €210 billion, up from €150 billion in 2010 and projected to reach €403 billion by 2018, with an approximate compound growth rate of 4.4% per year. Western Europe represents approximately 25% of the global MD market, with Germany leading the market followed by France, the UK and Italy (Cunningham *et al*., 2015). However, there are still important challenges that currently face the licencing and reimbursement pathways of MDs. Much criticism has been raised, for instance, by a number of high-profile device recalls in recent years (Thompson *et al*., 2011; Zuckerman *et al*., 2011), because of safety issues that have included breast implants (Lahiri andWaters, 2006), specific types of artificial hips (Curfman and Redberg, 2011) and implantable cardioverter-defibrillator leads (Maisel, 2008).

In response to this ongoing debate, we undertook a comprehensive review of current international licencing and HTA practices for MDs. Our research highlights a number of important findings. First, although we observed differences in the balance of requirements across regulators in their reliance of pre-market and post-market approval, our study confirms that, across the globe, current regulatory processes are often substantially less stringent than drugs. This claim was for the first time confirmed by the comparative assessment of MD HTA reports versus drug HTA reports, showing a significantly higher proportion of MD reports including observational and non-RCT evidence based on smaller clinical studies. Whilst there is currently no single harmonised international classification for devices, regulators appear to consistently relate their evidential requirements for licencing to the level of patient risk associated with the use of different categories of device. For example, the US FDA is more likely than other international regulators to require a pre-market RCT for a high-risk (e.g. class III) implantable product.

Second, our interviews with HTA agencies and review of their reports confirmed that this lack of clinical evidence generated in response to regulatory requirements for MDs leads to difficulties in conducting HTAs, which in some jurisdictions can create delays in funding and patient access. Such challenges include capacity or expertise gap and methodological difficulties in the use of observational data to make reliable effectiveness and cost-effectiveness assessment for a device. This particular aspect is illustrated by the lower methodological quality observed in MDs HTA reports than drug reports as shown in our comparative study.

Table V. Policy recommendations made by health technology assessment reports[b]

	Drug ($N = 18$)	Device ($N = 27$)	Drug versus device
	n (%)	*n* (%)	*P*-value[a]
Recommended	1 (20)	0 (0)	0.26
Optimised	1 (20)	5 (83)	
Only in research	1 (20)	0 (0)	
Not recommended	2 (40)	1 (17)	
Not reported	13 (72)	21 (78)	

[a]Chi-squared test.
[b]Categorised according to the National Institute for Health and Care Excellence technology appraisal decision outcomes.

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Third, many HTA agencies have developed specific organisational structures and processes for the handling of their evaluation of devices. Heterogeneity of agency procedures is a disadvantage for manufacturers who need to set up and prepare for different submissions. Nevertheless, we found little or no evidence of the application of HTA methodologies to quantitatively take account of the specificities of devices. When looking at the empirical application of methods in HTA reports, we found that MD reports are more likely than drug reports to consider organisational aspects of the implementation of health technologies in confirmation of the critical role played by setting-related, institution-related and operator-related aspects in shaping devices' effectiveness. Although HTA reports often acknowledged MD-specific issues (i.e. organisational factors, learning curve and combination of observational and trial evidence), however and quite disappointingly they fail to assess the impact of these MD-specific technology issues in terms of their quantitative impact on cost-effectiveness of the device or uncertainty.

Whilst the systematic approach to the selection, data extraction and analysis of included HTA reports strengthens the findings of our study, the relatively small number of eligible documents, published in the English language and related to cardiovascular disease, may not be generalisable across other medical conditions. However, given the relevance of MD technologies in cardiovascular disease both economically and therapeutically, it is likely that if any methodological development in the evaluation of devices is adopted, it will be implemented in this specific disease area. Additional comparative analyses of drug versus MD HTA reports in other medical conditions may help clarify our findings.

Our findings have important implications for both regulators, HTA decision makers, manufacturers and clinical researchers in order to improve and speed up the process of assessment, thereby securing faster patient access for those devices that can be shown to be safe and cost-effective. First of all, whilst it seems appropriate that the type of evidence required prior to approval should match the potential risk of a new device, more stringent requirements to provide clinical data for the efficacy and safety are needed for moderate-risk to high-risk devices. Appropriate methodological choices should be implemented in order to choose trial designs that allow to tackle specific challenges raised by the clinical evaluation of MDs (Bernard *et al*., 2014). Linked to this is the need for international harmonisation of regulatory requirements, with efforts to set common risk classification rules. Furthermore, post-marketing surveillance is particularly important in the case of devices, not just for safety monitoring but also to go beyond efficacy demonstrated in a trial setting and assess effectiveness in regular use. Collection and promotion of access to device and user real-world data should be encouraged to provide additional information not only on adverse events but also on learning curve and organisational impact of MDs, to facilitate reassessment of the technology when it becomes established in the routine practice. There is the need and the opportunity for better linkage between current licencing and HTA processes. Although the objectives of licensors and HTA bodies are distinct, in most international jurisdictions it is HTA that drives healthcare system funding and therefore acts as the *de facto* barrier to MD access (Tsoi *et al*., 2013). This is particularly true for devices first licenced in the EU where manufacturers will often be faced with developing further clinical and economic evidence for HTA bodies in order to secure reimbursement. The system of approval based on substantial equivalence (e.g. the US 510(k) approval process) has already been recommended to be replaced with an integrated pre-market and post-market regulatory framework that effectively provides a reasonable assurance of safety and effectiveness throughout the device life cycle (Heneghan and Thompson, 2012; Sorenson and Drummond, 2014). A potential collaborative model of future device regulation is the MaRS Excellence in Clinical Technology Evaluation (EXCITE) programme currently operating in Ontario (MaRS, 2011). In the EXCITE programme, device manufacturers can have discussions with both regulators (Health Canada) and HTA (Ontario Office of Health Technology) bodies in order to co-design clinical trial protocols to meet the needs of both the regulator and the HTA body. A 'parallel submission' to both decision-making authorities is then encouraged and supported. Ongoing EXCITE device projects include electrical stimulation for upper limb movements in stroke patients, home sleep apnea event detector and RNA disruption assay for early prediction of complete response to chemotherapy in breast cancer patients (Levin, 2015). In 2010, the US FDA and the Centers for Medicare and Medicaid Services proposed a partial alignment of their respective review processes for new medical products. The two institutions have recently announced that they will be

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implementing and extending indefinitely the Parallel Review of MDs pilot programme, thus allowing product sponsors who seek a national coverage determination from the Centers for Medicare and Medicaid Services to request that the review begins earlier, concurrently with the later stages of the FDA review process. The proposed aligned system of evidence generation is believed to lead to time-saving, uncertainty reduction in the clinical development path and faster market uptake but also to promote better evidence generation that addresses simultaneously the information needs of regulators, payers, patients and clinicians (Messner and Tunis, 2012). In Europe, the Shaping European Early Dialogues project has been developed as a pilot platform to facilitate the opportunity of early dialogue with the regulator (i.e. European Medicines Agency), selected European HTA agencies and industry (Harousseau *et al*., 2015). Of the 11 early dialogues performed so far, three have concerned MD submissions. A relatively simple but potentially highly effective initiative has been for regulators to make their documents and processes more available to HTA bodies (Berntgen *et al*., 2014).

The health service research community needs to extend existing RCT and HTA methods to effectively take account of the specific issues of devices. The importance of such methodological innovation is highlighted in the recent guideline for MDs developed by EUNetHTA (EUnetHTA, 2015). Two examples of methodological developments for handling of device-specific issues produced from the MedTecHTA programme are detailed in other contribution to this *Health Economics* supplement (Schnell-Inderst *et al*., 2017; Varabyova *et al*., 2016). Relatedly, a development of the necessary capacity within the HTA agencies is needed in order to implement these under-used approaches.

Current licencing and HTA systems are continuously evolving with the specific aims of assessing safety, performance, efficacy, effectiveness and added value of health technologies, including MDs. Little harmonisation has been observed so far between the two, whilst based on the findings of our research projects, we would encourage a continuous dialogue among all parties involved to agree on the types of clinical and health economic evidence needed for licencing and for funding to new devices, to strengthen the evidence base and the development and application of innovative HTA methodologies and to shorten the overall time needed for patients to access cost-effective devices.

APPENDIX A: SEARCH STRATEGY

#1	(*) and (Full publication record: ZDT) IN HTA FROM 2008 TO 2013
#2	MeSH DESCRIPTOR cardiovascular diseases EXPLODE ALL TREES
#3	#1 AND #2

APPENDIX B: DATA EXTRACTION TOOL, FIELDS AND CODING

	Field name	Type	Description
1	ID	Continuous	Unique identifier
2	RevName	Open-ended	Name of researcher performing data extraction
3	ExDate	Open-ended	Date of extraction
4	Date	Date/time	Date of publication
5	Record	Continuous	Corresponding search record number set by the Centre for Reviews and Dissemination
6	Agency	Open-ended	Name of agency publishing HTA report
7	Country	Open-ended	Name of country publishing HTA report
8	Invent	Categorical	Type of intervention: • Drug or • Medical Device
9	Class	Open-ended	Device assignment to a specified regulatory class based on the level of control necessary

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	Field name	Type	Description
			to assure the safety and effectiveness (e.g. Class I, Class II and Class III)
10	Therapy	Categorical	Cardiovascular therapy area targeted by the intervention: • Cerebrovascular • Coronary or • Peripheral
11	Problem	Open-ended	Decision problem addressed in HTA report
12	Participants	Open-ended	Patient, population of patients, problem
13	Intervention	Open-ended	List interventions, indicate if STA (single technology assessment) or MTA (multiple technology assessment)
14	Outcomes	Open-ended	List of all outcomes evaluated in report
15	Comparators	Open-ended	Comparison (another therapy or placebo)
16	Licensing	Date/time	Date of licencing
17	Clinical	Open-ended	Type of clinical studies included
18	Clinical_num	Open-ended	Number of studies (by type, e.g. RCT or non-RCT)
19	Clinical_patient	Open-ended	Number of patients included in each clinical scenario bucket
20	Econ	Open-ended	Type of economic evaluation included
21	Econ_num	Open-ended	Number of each type of economic evaluation
22	Design1	Binary	Systematic review of clinical outcomes (yes/no)
23	Design2	Binary	Systematic review without meta-analysis (yes/no)
24	Design3	Binary	Systematic review with meta-analysis (yes/no)
25	Design4	Binary	Include economic evaluation/economic model (yes/no)
26	Amstar1	Categorical	A Measurement Tool to Assess Systematic Reviews (AMSTAR) Checklist Item 1: Was an '*a priori*' design provided, • No • Yes • Can't answer • Not applicable
27	Amstar2	Categorical	A Measurement Tool to Assess Systematic Reviews (AMSTAR) Checklist Item 2: Was there duplicate study selection and data extraction? • No • Yes • Can't answer • Not applicable
28	Amstar3	Categorical	A Measurement Tool to Assess Systematic Reviews (AMSTAR) Checklist Item 3: was a comprehensive literature search performed? • No • Yes • Can't answer • Not applicable
29	Amstar4	Categorical	A Measurement Tool to Assess Systematic Reviews (AMSTAR) Checklist Item 4: Was the status of publication (i.e. grey literature) used as an inclusion criterion?
30	Amstar5	Categorical	A Measurement Tool to Assess Systematic Reviews (AMSTAR) Checklist Item 5: Was a list of studies (included and excluded) provided? • No • Yes • Can't answer • Not applicable

(*Continues*)

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	Field name	Type	Description
31	Amstar6	Categorical	A Measurement Tool to Assess Systematic Reviews (AMSTAR) Checklist Item 6: Were the characteristics of the included studies provided? • No • Yes • Can't answer • Not applicable
32	Amstar7	Categorical	A Measurement Tool to Assess Systematic Reviews (AMSTAR) Checklist Item 7: Was the scientific quality of the included studies assessed and documented? • No • Yes • Can't answer • Not applicable
33	Amstar8	Categorical	A Measurement Tool to Assess Systematic Reviews (AMSTAR) Checklist Item 8: Was the scientific quality of the included studies used appropriately in formulating conclusions? • No • Yes • Can't answer • Not applicable
34	Amstar9	Categorical	A Measurement Tool to Assess Systematic Reviews (AMSTAR) Checklist Item 9: Were the methods used to combine the findings of studies appropriate? • No • Yes • Can't answer • Not applicable
35	Amstar10	Categorical	A Measurement Tool to Assess Systematic Reviews (AMSTAR) Checklist Item 10: Was the likelihood of publication bias assessed? • No • Yes • Can't answer • Not applicable
36	Amstar11	Categorical	A Measurement Tool to Assess Systematic Reviews (AMSTAR) Checklist Item 11: Was the conflict of interest included?
37	Drummond1	Binary	Drummond checklist for assessing economic evaluations item 1: Was a well-defined question posed? (yes/no)
38	Drummond2	Binary	Drummond checklist for assessing economic evaluations item 2: Was a comprehensive description of the competing alternatives given? (i.e. can you tell who did what to whom, where and how often? (yes/no)
39	Drummond3	Binary	Drummond checklist for assessing economic evaluations item 3: Was the effectiveness of the programmes or services established

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	Field name	Type	Description
40	Drummond4	Binary	Drummond checklist for assessing economic evaluations item 4: Were all the important and relevant costs and consequences for each alternative identified? (yes/no)
41	Drummond5	Binary	Drummond checklist for assessing economic evaluations item 5: Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost work-days and gained life-years)? (yes/no)
42	Drummond6	Binary	Drummond checklist for assessing economic evaluations item 6: Were costs and consequences valued credibly? (yes/no)
43	Drummond7	Binary	Drummond checklist for assessing economic evaluations item 7: Were costs and consequences adjusted for differential timing? (yes/no)
44	Drummond8	Binary	Drummond checklist for assessing economic evaluations item 8: Was an incremental analysis of costs and consequences of alternatives performed? (yes/no)
45	Drummond9	Binary	Drummond checklist for assessing economic evaluations item 9: Was allowance made for uncertainty in the estimates of costs and consequences? (yes/no)
46	Drummond10	Binary	Drummond checklist for assessing economic evaluations item 10: Did the presentation and discussion of study results include all issues of concern to users? (yes/no)
47	Drug_specs	Open-ended	Technology-specific methods and considerations for drugs (e.g. oral versus injectable)
48	Device_specs	Open-ended	Technology-specific methods and considerations for devices (e.g. learning curve, incremental evolution)
49	Uncertainty_cl	Binary	Did the clinical analysis take uncertainty into account? (yes/no)
50	Uncertainty_cl2	Open-ended	If yes to Item 59, how did the clinical analysis take uncertainty into account?
51	Uncertainty_ee	Binary	Did the economic analysis take uncertainty into account? (yes/no)
52	Uncertainty_ee2	Open-ended	If yes to Item 61, how did the economic analysis take uncertainty into account?
53	Res_Core1	Binary	Indicate if this element of HTA Core Model is reported in the results: Health problem and current use of technology (yes/no)
54	Res_Core2	Binary	Indicate if this element of HTA Core Model is reported in the results: Description and technical characteristics of technology (yes/no)
55	Res_Core3	Binary	Indicate if this element of HTA Core Model is reported in the results: Safety (yes/no)
56	Res_Core4	Binary	Indicate if this element of HTA Core Model is reported in the results: Clinical effectiveness (yes/no)
57	Res_Core5	Binary	Indicate if this element of HTA Core Model is reported in the results: Cost and economic evaluation (yes/no)
58	Res_Core6	Binary	Indicate if this element of HTA Core Model is reported in the results: Ethical aspects
59	Res_Core7	Binary	Indicate if this element of HTA Core Model is reported in the results: Organisational aspects (yes/no)
60	Res_Core8	Binary	Indicate if this element of HTA Core Model is reported in the results: Social aspects (yes/no)
61	Res_Core9	Binary	Indicate if this element of HTA Core Model is reported in the results: Legal aspects (yes/no)

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	Field name	Type	Description
62	Clinical_mort	Continuous	All-cause mortality reported results (including confidence interval and standard error) (yes/no)
63	Clinical_primary	Open-ended	Primary outcome/first reported
64	Clinical_primary_res	Continuous	Primary outcome/first reported results (including confidence interval and standard error)
65	Econ_base	Continuous	Economic evaluation base case result
66	Conclusion	Open-ended	Report conclusion or policy recommendation
67	Device_recs	Open-ended	Any device specific recommendation

CONFLICT OF INTEREST

The authors have no conflict of interest.

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