

Critical Appraisal of Systematic Reviews of Implantable Medical Devices

Version [#]

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Abstract

Background: The use of medical devices in clinical practice is widespread and has a profound impact on patient management. Issues unique to evaluation of medical devices in research can include technical complexity and evolution, combined with practitioner variability and operator learning curve. However, empirical research on the comparative effectiveness of medical devices has lagged behind the innovations in medical device technologies.

Methods: We conducted a critical appraisal of systematic reviews focusing on implantable medical devices. We convened a Technical Expert Panel (TEP) who helped to refine scope of the project. The TEP also identified device categories, and provided feedback on the methodological approach. Five implantable medical device categories were reviewed in the present report: cardiac implantable devices (e.g., pacemakers or defibrillators), vascular interventional devices (e.g., stents or prosthetic vascular grafts), orthopedic implants (e.g., prosthetic disc replacement), skin-replacement grafts (e.g., wound care products), and neurostimulators (e.g., spinal or deep brain neurostimulator). Searches were conducted in MEDLINE® and the Cochrane Database of Systematic Reviews to identify recent systematic reviews published from January 2009 to December 2010, using key words for each of the five categories of implantable medical devices. Two of the five groups yielded limited number of reviews namely skin-replacement grafts (2 reviews) and cardiac implantable defibrillators (9 reviews). We searched back to 2004 to identify additional eligible reviews related to these topics. We extracted information on types of devices and types of studies covered, methods for literature synthesis and quality assessment, availability of data, and statistical analyses performed. The extraction covered 30 items relevant to the evaluation of all systematic reviews as identified in the MOOSE and PRISMA guidelines, in addition to 8 device- and procedure-specific items relevant to the evaluation of implantable medical devices.

Results: Our searches retrieved 467 citations, of which 181 systematic reviews met eligibility criteria. Of these reviews, 19 evaluated cardiac implantable devices, 124 evaluated vascular devices, 16 evaluated orthopedic implants, 8 evaluated skin-replacement grafts, and 14 evaluated neurostimulators. Of the eligible systematic reviews, 123 conducted meta-analyses and the remaining 58 conducted qualitative syntheses; 66 reviewed only trials, 51 reviewed observational studies, 56 reviewed both, and eight reviews did not explicitly mention the study designs of primary studies included. Of the 38 recommended items our analyses found that only 12 were commonly reported. While search terms, years searched, inclusion or exclusion criteria, population at baseline, description of intervention, and types of studies included were frequently reported, less consistent information was obtained regarding searches or inclusion of studies in more than one language (34 percent) and whether a grey literature search was performed (44 percent). Other items that were infrequently reported were provision of a literature flow diagram (44 percent), a discussion of costs or cost-effectiveness (23 percent), evaluation of risk of bias (43 percent) and an assessment of the overall strength of the body of evidence (18 percent). Device-specific information such as generalizing results from one device to a similar device (36 to 47 percent of the time) and evolution of technology (21 percent) were infrequently reported. Operator-specific information including training of provider, evaluation of team expertise overall, and volume at operating site were rarely reported. The quality of reporting varied across device categories mostly in terms of device-specific information and handling of heterogeneity.

There were also no significant differences in quality of reporting when reviews were stratified by authors' affiliation to industry.

Conclusion: We evaluated 181 recent systematic reviews on implantable medical devices. These reviews generally lack data on the reporting of some important generic items applicable to any systematic review. We also found infrequent reporting of information specific to the study of implantable medical devices including differences in device and operator characteristics, and device evolution over time. This review highlights the need for a systematic inclusion of items as outlined in the PRISMA and the MOOSE statements when performing any review. Several issues unique to the evaluation of medical devices can potentially impact study outcomes and interpretation of results. In addition, the interventions (devices) can vary appreciably across primary studies included or continue to evolve overtime during study period. Systematic reviews of implantable medical devices need to incorporate device- or operator-specific data.

Background

Advances in medical devices have profoundly transformed clinical practices.¹ However, empirical research on the comparative effectiveness of medical devices has lagged behind the innovations in medical device technologies. An editorial review found that published research studies of medical devices suffer from a lack of transparency of study findings, device-related complications, and author conflicts of interest.² According to a recent position paper, the key areas that are potentially underrepresented in the comparative effectiveness of medical devices are methodological evaluation of study design and evaluation of factors that affect comparative safety and effectiveness. These factors include a lack of standardization of outcomes and endpoints, evaluation of device–operator interactions, and evaluation of characteristics of the clinical practice setting.³ There is a lack of methodological research to guide the assessments of medical devices. Evaluation of medical devices in research can have inherent, unique issues—such as technical complexity as well as practitioner variability, operator learning curve, and evolution of a device during study period—that can potentially impact study outcomes.

Systematic reviews have established their role in the realm of medical practice and research. Clinicians use systematic reviews to keep abreast of current research and to provide information on the efficacy of competing interventions. Granting agencies utilize systematic reviews to prioritize and to justify funding. Healthcare organizations use review findings to shape policy and inform clinical practice guidelines.^{4,5} Despite the many publications of systematic reviews of medical devices, this topic has not undergone an empirical evaluation. A thorough empirical appraisal of systematic reviews is needed to critically assess current practices and to identify issues and gaps of reporting. The information generated could potentially be used to develop new items in reporting guidelines, and to improve the conduct and the quality of reporting of systematic reviews of medical devices. The strength of systematic reviews relies on the rigor of the methods and the clarity of reporting as well as the conduct and validity of the included primary studies. Issues and gaps in reporting of systematic reviews of medical devices can also directly reflect limitations pertaining to primary data. Therefore, results from a critical appraisal of systematic reviews could also guide what must be done going forward to address issues and gaps in primary data.

One large body of devices of interest is implantable medical devices. The Food and Drug Administration (FDA) defines these as devices that are partly or completely inserted into the body or a natural orifice using surgical or medical procedures and is expected to remain in the body or orifice for at least 30 days (or permanently).⁶ Such devices can be removed only surgically or deactivated medically. Implantable devices also include those that are used to replace an epithelial or eye surface.⁶ The demand for implantable medical devices in the United States is projected to increase 8.3 percent annually to \$49 billion in 2014, with the fastest-growing categories being spinal implants, cardiac implants, and orthobiologics.⁷ These increases in device implantation are a result of the aging population. For example, an estimated 200,000 hip replacements surgeries are performed in the U.S. each year in elderly patients.⁸ The prevalence of functioning cardiac devices such as permanent pacemakers is estimated to be over 3 million worldwide.⁹

As the Evidence-based Practice Center (EPC) designated for the cross-cutting concentration of diagnostic testing, imaging technologies, and medical and assistive devices, we conducted a critical appraisal of systematic reviews of implantable medical devices. The goals of this project were to evaluate published systematic reviews and meta-analyses to understand the

methodologies employed; identify current strengths, limitations, deficiencies and unique challenges; and make recommendations to improve future conduct and reporting of systematic reviews of implantable medical devices. The findings from such an appraisal of systematic reviews could be used to inform a broad range of stakeholders, including researchers, clinicians, guideline developers, policymakers, and payers. Some implantable medical devices are frequently used in clinical practice and are expensive. Therefore, to cover these highly utilized devices, and on the basis of the recommendations of the Technical Expert Panel (TEP), we chose to focus on five broad implantable medical device categories in the present report: cardiac implantable devices, vascular interventional devices, orthopedic implants, skin-replacement grafts, and neurostimulators.

Methods

We conducted a critical appraisal of methodologies employed and the reporting of information in published systematic reviews and meta-analyses of implantable medical devices. We convened a Technical Expert Panel (TEP) to help identify devices, refine key questions, and to comment on the methodological approach.

Technical Expert Panel

The TEP, a group of eight national experts, was assembled to provide advice regarding the scope of the project. Members included private and public payers, industry representatives, an FDA representative, and the Task Order Officer from AHRQ. The EPC held teleconferences with the TEP, which served strictly in an advisory capacity to identify the device categories, to assist in the development of project's scope and Key Questions, and to define parameters for the methodology of the critical appraisal. After discussions with the TEP and AHRQ, the following five implantable medical device categories were selected for analyses: cardiac implantable devices (e.g., pacemakers or defibrillators), vascular interventional devices (e.g., stents or prosthetic vascular grafts), orthopedic implants (e.g., disc replacement), skin-replacement grafts (e.g., wound care products), and neurostimulators (e.g., spinal or deep brain neurostimulator).

Key Questions

The following key questions were formulated in consultation with the TEP and AHRQ. For each of the proposed Key Questions, with input from the TEP, we operationalized our analysis by creating specific items that could be answered by the systematic reviews (Table 1).

1. How are published systematic reviews of implantable medical devices conducted and reported for items such as literature searches, study selection, and results (per items from the PRISMA and MOOSE)?
2. a) What are the issues unique to systematic reviews of implantable medical devices? b) How are heterogeneity handled in published systematic reviews of medical devices?
3. What are the limitations and issues related to the quality and generalizability of the systematic reviews of implantable medical devices?

Literature search

Critical appraisal of large numbers of implantable medical devices can be challenging since there are many published systematic reviews. Our objective was to evaluate approximately 200 recently published systematic reviews (deemed a priori as a feasible number). To reach this target, we limited our search to recent reviews as they are more likely to be relevant and adhere to published reporting standards. Searches were conducted in MEDLINE® and the Cochrane Database of Systematic Reviews to identify systematic reviews published from January 2009 to December 2010, using key words for each of the five categories of implantable medical devices (Appendix 1). No language restriction was applied.

Potentially relevant reviews were those articles in which the abstracts described searches or eligibility criteria for study identification or included terms such as “systematic,” “evidence,” “evidence-based,” “meta-analysis,” or “pooled analysis.” We included all eligible systematic reviews published within 2 years (from January 2009 to December 2010) for all topics. Our initial search identified a limited number of reviews for two of the five groups, namely skin-replacement grafts (2 reviews) and cardiac implantable defibrillators (9 reviews). In consultation with the Task Order Officer at AHRQ, we searched back to 2004 to identify additional eligible reviews related to these topics.

Eligibility criteria and citation screening

There are no commonly agreed-upon criteria for defining a systematic review. For the purpose of this report, a systematic review was defined as a publication that contained at least two of the following three components: a statement of the research questions (or aims or objectives), a description of the literature search, and a list of study-eligibility criteria. This approach was used in a previous empirical paper that considers these three components to identify a systematic review.¹⁰ During full-text screening, we noted that many published systematic reviews of implantable medical devices did not clearly report all three basic components. We did not contact authors for clarifications of these three components. Therefore, we used a liberal definition (at least two of the three components) in order to include a maximum number of current systematic reviews.

We included systematic reviews of any design (randomized trials, nonrandomized comparative studies, or observational studies) and methodology for synthesis (qualitative or quantitative synthesis including meta-analyses of individual patient data). We included all reviews published within this time period, which could potentially include multiple reviews on the same topic or different reviews published by the same team of researchers. However, we did not include duplicate publications or similar reviews by the same team of researchers.

There were no specific sampling criteria per device category. Though an even distribution of reviews across the five implantable medical device categories would be preferable, this could not be achieved because of a large number of articles reviewing vascular interventional devices, in particular stents. The TEP concurred with the approach of selection of reviews without specific sampling criteria.

We assessed titles and/or abstracts of citations identified from literature searches for potentially relevant systematic reviews. The titles and/or abstracts were screened by one researcher. Abstracts tagged “reject” by a researcher were rescreened by a second researcher. Full-text articles of abstracts that met screening criteria were retrieved and examined by two independent reviewers to confirm their eligibility according to predetermined criteria. All disagreements were resolved in consultation with a senior reviewer. The reasons for excluding systematic reviews were tabulated. In this report, we did not evaluate the primary studies included within the systematic reviews. A list of included and excluded full-texts is available at the end of the text.

Data extraction

There have been attempts to improve the general quality of reporting of systematic reviews through guidelines such as PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and MOOSE (Meta-analysis of Observational Studies in Epidemiology).^{11,12} We used the current guidelines of reporting of systematic reviews and meta-analyses to come up with a list of information items to collect from the published systematic reviews to answer the Key Questions. The operational definitions of each item are described in Table 1.

Currently, there are no specific tools or checklists to evaluate the reporting quality of systematic reviews of implantable medical devices. We consulted the TEP to identify device- and procedure-specific information that is relevant and important to the evaluation of these devices. We identified 8 device- and procedure-specific information items in addition to the 30 systematic review-specific information items identified in the MOOSE and PRISMA guidelines (Table 1 under items reported for Key Question 2).

A standardized form using Google™ docs was used for data extraction.¹ The basic elements and design of the form were customized to capture all the relevant elements of the Key Questions. We tested the form on several reviews and revised it as necessary before beginning full data extraction of all articles. The data-extraction fields are presented in Appendix 2. Each systematic review was extracted by one reviewer that was reviewed and confirmed by at least one other reviewer. Disagreements were resolved through consensus in consultation with a third reviewer. Extracted data were exported to Microsoft Excel®.

Data synthesis

Results and data in the tables were organized on the basis of reporting items for each Key Question. The unit of analysis was the systematic review article. Descriptive analyses were performed and summary statistics calculated regarding the reporting characteristics of systematic reviews. Analyses include whether the reporting followed published guidelines for reporting of systematic reviews and meta-analyses, the reporting of device- or procedure-specific information, the number and types of primary studies analyzed, quality assessment of primary studies, methods for quantitative syntheses, descriptions of heterogeneity and generalizability, and protocols for reporting of results. Handling of heterogeneity included items that were evaluated within systematic reviews as quantitatively (e.g., models for meta-analyses and sensitivity analyses), and either quantitatively or qualitatively (e.g., assessment of heterogeneity and results by subgroups).

We compared key methodological and reporting aspects of reviews pertaining to the five groups of implantable medical devices. These comparisons were performed using the Fisher exact test for categorical variables or the Kruskal-Wallis test for continuous and count variables. Additional subgroup analyses of key methodological and reporting aspects of reviews were conducted comparing systematic reviews of observational studies to those of interventional studies, comparing reviews that conducted a quantitative with qualitative syntheses, and comparing reviews that reported authors' ties to device industry with those that did not. All quantitative analyses were performed with Excel® and Stata 11® (Stata Corp., College Station, TX). All P-values are two-tailed and considered to indicate significance if less than 0.05; no

¹ The live form can be viewed and tested here: <http://bit.ly/nhK0gl> (last accessed on 08/08/2011)

adjustments for multiple comparisons were performed. The P-value of <0.05 indicates that there is a difference in reporting items between the groups compared. Additional subgroup analyses were conducted for each of the five groups of implantable medical devices.

Table 1. Reporting items for systematic reviews of implantable medical devices

Reporting Item	Definition for Adequate Reporting
Items for Key Question 1	
Search terms	Keywords for identifying relevant studies for the research questions (i.e., population, interventions, comparator, and outcomes [PICO]), or complete search strategy (e.g., keywords, medical subject headings) were described or referred to elsewhere.
Searches in multiple databases	Search was conducted in more than one electronic database.
Search years	Time period of the articles searched and included was explicitly described.
Searches in multiple languages	Search was conducted in English and other languages.
Searching for unpublished data	Authors explicitly stated the efforts to include unpublished data (e.g., contact with authors, meeting abstracts or conference preceding, dissertations, or grey literature search).
Inclusion or exclusion criteria	Definitions of at least two of the PICOS criteria (e.g., randomized controlled trials of drug-eluting stents were included) were reported.
Baseline description of the population	Health status of the population at baseline (i.e., hypertension, diabetes, or coronary artery disease).
Types of interventions/exposures	Interventions or exposures were described (usually includes device name, or a brief description, or type of device).
Types of comparators	Comparators were described (can include another device, or medical treatment, or surgical treatment).
Types of outcomes	Outcomes or endpoints were defined.
Types of study designs	Design of the included studies was described.
Number of included and excluded studies	Number of eligible and ineligible studies identified from the search was reported.
Reasons for exclusion	Reasons for exclusions were described.
Flow diagram for the number of included and excluded studies	A flow diagram showing the progress of study selection was presented.
The total number of primary studies included in the systematic review/meta-analysis	The total number of studies that met inclusion criteria was reported in the text, tables, or figures.
Graphical presentation of the results	Graphics (e.g., forest plot, trend in outcomes over time, and regression plots) summarizing individual study estimates and overall estimates were presented.
Meta-analyses were performed	Description of whether a meta-analysis was performed.
Costs or cost-effectiveness	Specific mention of costs of devices or analyses of cost-effectiveness
Items for Key Question 2	
Device or operator-specific	
Data on differences across device characteristics were discussed	When multiple devices are used, the differences among devices (e.g., sirolimus-eluting stents, paclitaxel-eluting stents, or bare-metal stents) were discussed across primary studies included.
Data on differences within device characteristics were available	Differences within devices (e.g., differences in programming within implantable cardiac defibrillator) were discussed across primary studies included.
Evolution of devices over time were discussed	Discussions within systematic reviews about evolution (change or development) of devices across primary studies evaluated.
Details of training/certification of operator were reported	Details within systematic reviews can include training, prior experience in procedures performed, or any other performance standards.
Ramp-up in provider technique (i.e. learning curve) was discussed	There was a relevant discussion about how the surgeon's experience with the device may affect outcomes.
Level of expertise of team/site were considered	Discussions were made related to the levels of expertise of a team within hospital where operators practice that may impact outcomes.
Continued ...	

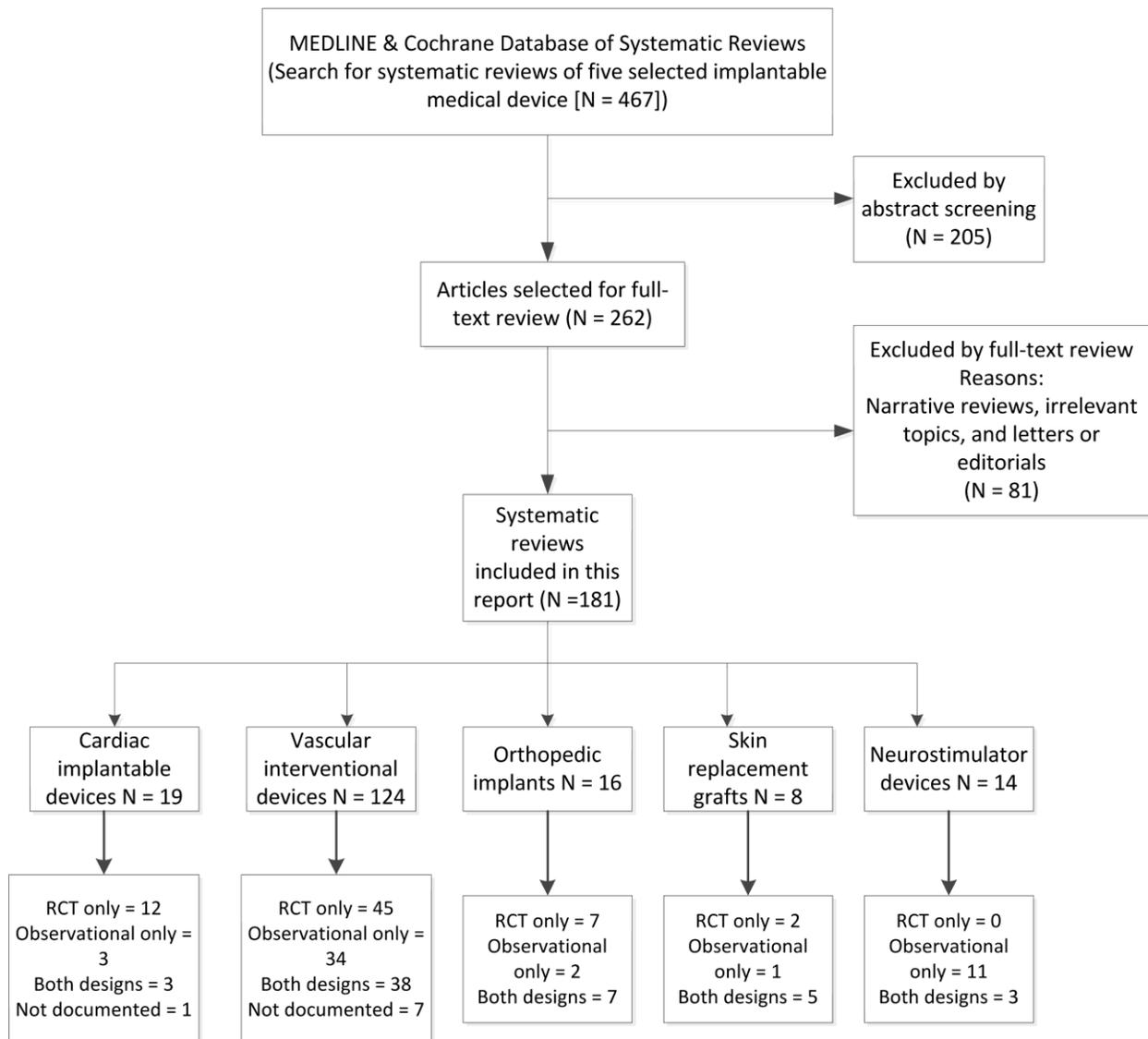
Table 1 continued

Reporting Item	Definition for Adequate Reporting
Items for Key Question 2 continued	
Practitioner variability were discussed	Variability among operators because different sets of operators are involved in each arm of the trial was discussed
"Volume at sites" effect were discussed	There was a relevant discussion about how site experience with the device may affect outcomes
Handling of heterogeneity	
Models for meta-analyses were reported	The methods of combining estimates (e.g., fixed- and random-effects models) were reported.
Meta-analyses used accepted methodology	Accepted methods were used when two or more studies were combined in meta-analysis or five studies or more studies were included in meta-regression analyses. Additionally studies were grouped by design or studies were grouped across similar interventions.
Heterogeneity was assessed or discussed	Sources of heterogeneity within population or among devices were discussed or quantified using statistical methods.
Sensitivity analyses were assessed	Details of the range of treatment estimates and confidence intervals resulting from the various sensitivity analyses were described.
Results by subgroups were considered or quantified	Potentially important subgroups were discussed (qualitatively) or quantified using accepted methods.
Items for Key Question 3	
Assessment of risk of bias	Potential impacts of the biases present in included primary studies were evaluated.
Publication bias was assessed	Quantitative assessment of publication bias (e.g., funnel plot, Begg and Egger tests) was used.
Use of specific checklist for quality items	The list of quality items for the validity (or quality) assessment of studies were applied and reported for each included study
Study limitations were described	Specific limitations either relating to primary studies or relating to the systematic review methodology was described
Overall strength of the body of evidence was assessed	Specific methods were used to assess the overall body of evidence (i.e., other than for example "strong evidence")
Specific future research recommendations were made	Specific suggestions for future research agenda (i.e., other than "more research is needed")
Funding source was declared	Specific funding source to conduct the systematic review was identified or when unfunded, this was made explicit.
Authors with ties to industry was reported	Reporting of authors of the systematic review being on the board or being employees of a device industry or having received current or previous funding from an industry relevant to the device reviewed.

Results

The searches in MEDLINE® and Cochrane Database of Systematic Reviews identified 467 citations, of which 262 full-text articles were retrieved and evaluated for their eligibility. A total of 181 systematic reviews met the eligibility criteria (Figure 1). Of these reviews, 19 evaluated cardiac implantable devices, 124 evaluated vascular devices, 16 evaluated orthopedic implants, 8 evaluated skin-replacement grafts, and 14 evaluated neurostimulators. Among eligible systematic reviews, 66 reviewed only trials, 51 reviewed observational studies, 56 reviewed both, and eight reviews did not explicitly mention the study designs of primary studies included.

Figure 1. Flow diagram of systematic reviews selection criteria



Key Question 1

How are published systematic reviews of implantable medical devices conducted and reported for items such as literature searches, study selection, and results (per items from the PRISMA and MOOSE)?

Reporting of literature searches, study selection, and results

This Key Question pertains to generic reporting aspects of reviews—items applicable to any systematic review including reviews of implantable medical devices. Overall results are presented in Table 2. Characteristics reported by nearly all (> 85 percent (median) of) reviews were search terms, years searched, inclusion or exclusion criteria, population at baseline, description of intervention, and types of studies included. These may be considered the core characteristics that are frequently reported within published systematic reviews of implantable medical devices. Among eligible reviews, infrequently reported items (less than 50 percent) were searches or inclusion of studies in more than one language (34 percent) and whether a grey literature search was performed (44 percent). No reviews reported on all 13 items relevant to search and selection criteria. Infrequently reported items for results included use of study flow diagram (44 percent) and a description of costs or cost-effectiveness of implantable medical devices (23 percent).

Table 2. Reporting of literature searches, study selection, and results in systematic reviews of implantable medical devices

Reporting area	Reporting Item	Total n (%) N=181
Search	Search terms were described or referred to elsewhere	165 (91)
	Multiple databases were searched	144 (79)
	Years searched were described	162 (89)
	Multiple languages were included in search	62 (34)
	Authors explicitly stated searching for unpublished data	80 (44)
Selection	Inclusion or exclusion criteria were stated	175 (96)
	Population at baseline was reported	181 (100)
	Interventions/exposures were described	181 (100)
	Comparators were described	152 (84)
	Outcomes were described	154 (85)
	Types of studies included were reported	174 (96)
	Number of studies included and excluded were reported	116 (61)
Reasons for exclusion were described	139 (76)	
Results	A flow diagram for the number of studies included and excluded was used	80 (44)
	The total number of primary studies included in the systematic review/meta-analysis was reported	1544
	Results were presented graphically	117 (64)
	Reviews that conducted a meta-analysis	124 (69)
	Costs or cost-effectiveness were described	42(23)

Reporting of items for Key Question 1 by device categories

The quality of reporting of literature searches and study selection was generally uniform across device categories (Table 3). Only 4 of 13 reporting items relevant to searches and study selection criteria were different across categories. These included performing searches in multiple databases, reporting of search dates, reporting of searches for unpublished data, and reporting of included and excluded studies. However, there were considerable differences across device categories for all reporting items of results including use of study flow diagram, graphical presentation of results, and description of costs or cost-effectiveness.

Table 3. Reporting of literature searches, study selection, and results in systematic reviews by device categories

Area	Reporting Item	Cardiac N=19	Vascular N=124	Orthopedic N=16	Skin grafts N=8	Neurostimulator N=14	P-value
Search	Search terms were described	17 (89)	113 (91)	16 (100)	7 (88)	12 (86)	0.12
	Multiple databases were searched	17 (84)	102 (82)	13 (81)	7 (89)	5 (36)	0.003
	Years searched were described	4 (20)	89 (72)	11 (69)	6 (75)	8 (57)	0.002
	Multiple languages were included in search	9 (47)	40 (32)	4 (25)	5 (63)	4 (29)	0.39
	Searching for unpublished data	15 (79)	58 (47)	2 (13)	3 (38)	2 (14)	<0.001
Selection	Inclusion or exclusion criteria were stated	19 (100)	119 (96)	15 (94)	8 (100)	13 (93)	0.31
	Population at baseline was reported	19 (100)	124 (100)	12 (75)	8 (100)	13 (93)	0.09
	Interventions/exposures were described	19 (100)	124 (100)	16 (100)	8 (100)	13 (93)	0.10
	Comparators were described	16 (84)	117 (94)	14 (88)	7 (89)	7 (50)	0.06
	Outcomes were described	19 (100)	124 (100)	16 (100)	8 (100)	13 (93)	0.10
	Types of studies included were reported	18 (95)	117 (94)	16 (100)	8 (100)	14 (100)	0.11
	Studies included and excluded were reported	14 (74)	84 (68)	10 (63)	4 (50)	4 (29)	0.03
	Reasons for exclusion were described	16 (84)	98 (79)	11 (69)	6 (75)	8 (57)	0.30
Results	A study flow diagram was used	13 (68)	59 (48)	5 (31)	2 (25)	1 (7)	0.008
	The number of primary studies included	248	234	300	284	478	NA
	Results were presented graphically	15 (79)	91 (73)	6 (38)	2 (25)	3 (21)	<0.001
	Reviews that conducted meta-analyses	15 (79)	99 (80)	7 (44)	1 (13)	3 (21)	0.06
	Costs or cost-effectiveness were described	10 (58)	19 (15)	5 (31)	6 (75)	3 (21)	0.001

Key Question 2

- a) *What are other issues unique to systematic reviews of medical devices?*
- b) *How are heterogeneity handled in published systematic reviews of medical devices?*

Reporting of device-specific information

Device-specific information was infrequently reported. Data on differences across devices were reported the most frequently, 47 percent of the time; about two thirds of reviews had no data differentiating within-device characteristics. A review would typically report data on devices (e.g., type of device and other device information) in a table describing their study and patient characteristics.

Evolution of devices was discussed in the reviews as one of the factors that may have affected the outcome of procedures. For example, the discussion section of a review would attribute evolution in angioplasty and stent catheters as one of the factors to positively influence procedural outcomes in recent primary studies as compared with “older” studies. However, this information was seldom directly assessed or reported in the results section of a systematic review. Additional examples of device-specific information that appeared in the discussion section of systematic reviews are provided in Table 5.

Table 4. Reporting of device- or operator-specific variables and handling of heterogeneity in systematic reviews of implantable medical devices

Reporting area	Reporting Item	Total n (%) N=181
Device-specific Variables	Data on differences across device characteristics were discussed	85 (47)
	Data on differences within device characteristics were available	64 (36)
	Evolution of devices over time were discussed	38 (21)
Operator-specific Variables	Details of training/certification of provider were reported	2 (1)
	Ramp-up in provider technique (i.e. learning curve) was discussed	13 (7)
	Level of expertise of team/site were considered	16 (9)
	Practitioner variability were discussed	18 (10)
	"Volume at sites" effect were discussed	14 (8)

Table 4 continued.

Reporting area	Reporting Item	Total n (%) N=181
Handling of heterogeneity	Models for meta-analyses were reported	123 (99)*
	Meta-analyses used accepted methodology (e.g. studies grouped by design or similar interventions)	114 (92)*
	Heterogeneity was assessed or discussed	139 (76)
	Sensitivity analyses were assessed or discussed	65 (52)*
	Results by subgroups were considered or quantified	92 (51)

*Among 181 eligible systematic reviews, 124 conducted a meta-analysis

Reporting of operator-specific information

Data on operator-specific information were rarely reported among included systematic reviews. When reported, they appeared most often in the discussion section. For example, only two reviews of vascular intervention category mentioned data regarding training or certification of the operator in their discussion section. The reviews described these as one of the factors influencing outcomes of the procedures. Table 6 lists selected examples of procedure-specific information in systematic reviews of implantable medical devices.

Reviews frequently discussed operators' learning curve and experience with device implantation as one of the factors that may be associated with temporal improvement in outcomes. Operator's learning curve or experience with device implantation was also discussed as a confounding variable that may have influenced outcomes. In order to allow sufficient experience with device implantation, some reviews restricted their eligibility criteria to studies that were published in later years. While most of the reviews discussed operators' experience and volume of the centers impacting outcome data, they rarely explored this variable in subgroup analyses.

Handling of heterogeneity

Overall, items infrequently reported were the assessment or discussion of a sensitivity analysis (52 percent), and presentation of results by subgroups (51 percent) (Table 4). The majority of the meta-analyses utilized accepted methodologies (92 percent). The remaining eight percent of the meta-analyses were performed by combining studies across designs.

Table 5. Examples of device-specific information that appeared in the discussion section of systematic reviews

<p><u>Device-specific information</u></p>
<p>“These findings could be explained by the difference in drug-release kinetics, with the sirolimus-eluting stent releasing almost all the sirolimus in the first 6 months, while more than 80% of the paclitaxel remains unreleased from the polymer coating of the paclitaxel-eluting stent, potentially resulting in more prolonged endothelial dysfunction and delayed healing with the latter.” (Roukoz 2009 PMID 19486720)</p>
<p><u>Evolution of devices over time</u></p>
<p>“However, it is premature to consider this conclusion definitive for several reasons. [Carotid artery stenting] technology and the technical expertise of operators currently performing the procedure are improving and are superior to those in the studies thus far reported.” (Paraskevas 2009 PMID 19698297)</p>
<p>“Since the last review was published 5 years ago and conducted over 9 years ago, new dressings may have been introduced and higher quality data published....It remains unclear which type of dressing is superior in terms of infection rate, healing quality, quality of life, and cost. It was difficult to compare moist and nonmoist dressings in this review because of the heterogeneity of the included articles.” (Voineskos 2009 PMID 19568092)</p>
<p>“Using meta-regression analysis, we found that the risks of CAS have decreased over time from 1993 to 2006. This may result from improvements in CAS technique, devices, or training and/or a better selection of CAS candidates over time. The development of devices to protect against embolism during the CAS procedure potentially constitutes an important advance.... However, there was significant heterogeneity across studies in this analysis. In fact, the apparent advantage of cerebral protection devices may be illusory. Indeed, the use of such protection devices has increased over time, and the apparent protective effect of those devices may have been confounded by advances in stenting technique and patient selection over time.” (Touze 2009 PMID 19892997)</p>

Table 6. Examples of operator-specific information that appeared in the discussion section of systematic reviews

<p>“The reason for the lower mortality rate in the DES group seen in our metaanalysis is unclear. It may be that DES, with known lower rates of restenosis, provides a true advantage over BMS....An alternative explanation may relate to a procedural learning curve, as operators may have become more technically proficient at unprotected LMCA PCI by the time DES were favored.” (Pandaya 2010 PMID 20630453)</p>
<p>“As a confounding variable, EPDs have been used more recently and therefore likely at a later stage of the operator’s learning curve.” (Roffi 2009 PMID 19861324)</p>
<p>“Our analysis suggests that centers with an experience of more than 16 stent graft procedures had a significantly higher success rate and a lower rate of complications than less experienced centers.” (Xiong 2009 PMID 19660348)</p>
<p>“These cases were done by a widely varied population of surgeons with varying skill and widely varied surgical technique. It is difficult to standardize the ability of these many surgeons and apply the results to the general population of surgeons practicing today.” (Winegar 2010 PMID 20594011)</p>
<p>“Most centers which have reported, as shown in our reference list, on their experience of surgical correction of thoracic scoliosis with pedicle screws come from very experienced surgeons. Therefore, this literature review may not reflect the reality of what happens in less-experienced centers or with surgeons going through their learning curve.” (Hicks 2010 PMID 20473117)</p>

Reporting of device- or operator-specific information by device categories

Device-specific information

In particular, these two items—discussions on differences across devices and discussions within devices—varied significantly according to device category (Table 7). This information appeared most often in the tables describing study and patient characteristics or in the discussion section rather than in the results or analyses section.

Cardiac implantable devices

Differences across devices and within devices were rarely reported across reviews of cardiac implantable devices. When reported, one or more of the device-specific information such as device type, method of implant, pacing mode, and position of the electrode were reported under study characteristics. Data related to evolution of devices and their role on applicability of trial results were mostly mentioned in the discussion section.

Vascular interventional devices

Compared with other device categories, reviews of vascular interventional devices more frequently reported device type or generation of device in the results or discussion sections. Few reviews conducted exploratory subgroup analyses to evaluate their short- and long-term efficacy. In addition to the discussions related to evolution of devices to explain heterogeneity in outcomes, some reviews used evolution of devices to define their eligibility criteria by excluding trials or data relating to “older” trials.

Orthopedic implants

In addition to the vascular interventional devices, systematic reviews of orthopedic implants reported device-specific information more frequently in the results or discussion sections than other device categories included. Details of devices were reported under study characteristics or the results section. Device-specific information included was one or more of the following: type of device, type of coating on the device number and location of device, surgical technique or

approach, and extraction and insertion torque. Only one review conducted exploratory subgroup analyses of these variables to evaluate their effect on treatment. Evolution of devices was often mentioned in the discussion or conclusion sections to explain good outcome data and progress achieved in clinical management.

Skin replacement grafts

Compared with other device categories, differences across devices were less frequently reported across systematic reviews of skin-replacement grafts. When reported device-specific information were frequently available in the results under device characteristics section. Data on differences within devices were reported in one-half of the reviews. Data on skin-replacement grafts reported were type of skin grafts, composition, and bioabsorbability or if they required removal. Only one review mentioned evolution of devices as the objective to conduct a new systematic review.

Neurostimulator devices

Compared with other device categories, differences across devices and within devices were less frequently reported across systematic reviews of neurostimulator devices. Information on differences within devices included stimulation parameter (frequency, intensity, and pulse width) and location of electrode placement across primary studies included. Data on differences across devices included only a mention of different types of devices without many details about different types of devices used across primary studies. Evolution of devices was discussed to explain differences in outcomes across primary studies included.

Operator-specific information

Only reviews of vascular interventional and orthopedic implants reported operator-specific information, while the other three categories did not. (Table 7) Only two vascular interventional reviews mentioned training or certification of the operator. In both these reviews, data relevant to training or certification of the operator were reported in the discussion section as one of the factors influencing outcomes of the procedures.

Reviews of vascular interventional noted that some primary studies included data only from centers with experienced operators or excluded data from first few patients due to a significant learning curve observed early in the study. In order to mitigate the impact of technical refinements and the procedural learning curve, one review defined their eligibility criteria by including studies that were published in later years.

While most of the reviews discussed operators' experience and volume in the centers impacting outcome data, reviews rarely explored this variable in subgroup analyses. Reviews that included observational studies discussed practitioner variability as one of the biases inherent to observational data.

Table 7 Reporting of device- or operator-specific variables and handling of heterogeneity in systematic reviews by device categories

Reporting area	Systematic reviews of implantable device by categories						P-value
	Reporting Item	Cardiac N=19	Vascular N=124	Orthopedic N=16	Skin grafts N=8	Neurostimulator N=14	
KQ 2							
Device-specific Variables	Differences across device characteristics were discussed	4 (21)	68 (55)	9 (56)	2 (25)	5 (36)	0.002
	Differences within device characteristics were available	1 (5)	48 (39)	9 (56)	4 (50)	3 (21)	0.002
	Evolution of devices over time were discussed	2 (10)	27 (22)	5 (31)	1 (13)	3 (21)	0.30
Operator-specific Variables	Details of training/certification of operator were reported	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)	1.00
	Learning curve of operator was discussed	0 (0)	12 (10)	1 (6)	0 (0)	0 (0)	0.60
	Level of expertise of team were considered	0 (0)	12 (10)	5 (31)	0 (0)	0 (0)	0.14
	Practitioner variability were discussed	0 (0)	16 (13)	2 (13)	0 (0)	0 (0)	0.35
	"Volume at sites" effect were discussed	0 (0)	12 (10)	2 (13)	0 (0)	0 (0)	0.47
Handling of heterogeneity	Models for meta-analyses were reported*	15 (100)	99 (100)	5 (71)	1 (100)	3 (21)	<0.001
	Meta-analyses used accepted methodology (e.g. studies grouped by design)*	15 (100)	89 (90)	7 (44)	1 (100)	3 (100)	<0.001
	Heterogeneity was assessed or discussed	8 (42)	88 (71)	6 (38)	3 (38)	1 (7)	0.10
	Sensitivity analyses were assessed*	12 (80)	46 (46)	4 (57)	1 (100)	1 (33)	0.008
	Results by subgroups were considered or quantified	15 (75)	65 (52)	8 (50)	2 (25)	2 (14)	0.007

* Results were analyzed based on 124 reviews that conducted meta-analyses

Key Question 3

What are the limitations and issues related to the quality and generalizability of the systematic reviews of implantable medical devices?

Reporting of validity, limitations, and future research recommendations

Outcomes evaluated were mostly clinical outcomes in 165 reviews (91 percent), surrogate outcomes in 66 reviews (36 percent), and 45 reviews (25 percent) evaluated both.

The items describing validity—evaluation of risk of bias (43 percent), the assessment for publication bias (48 percent), and methodological quality using checklists (40 percent)—were infrequently reported among eligible systematic reviews. Study limitations were given in 96 percent of reviews; 82 percent provided specific future research recommendations (i.e., more than stating that future research is simply needed) (Table 8). The reporting of quality items varied significantly across device categories (Table 9). The overall strength of the body of evidence was assessed in only 33 reviews (18 percent); this quality item varied significantly across device categories (Table 9).

Identification of a specific funding source and reporting of author ties to industry were less frequently reported. Of these, reporting of specific funding varied significantly across device categories.

Table 8. Reporting of validity and generalizability information in systematic reviews of implantable medical devices

Reporting area	Reporting Item	Total n (%) N=181
Validity	Risk of bias was assessed	79 (43)
	Publication bias was assessed	59 (48)*
	Quality items or checklists were applied and reported	72 (40)
Discussion	Study limitations were described	175 (96)
	Overall strength of the body of evidence was assessed	33 (18)
	Specific future research recommendations were made	149 (82)
	Funding source was identified	76 (42)
	Author ties to industry was reported	38 (21)

* Results were analyzed based on 124 reviews that conducted meta-analyses

Table 9. Reporting of validity and generalizability information in systematic reviews by device categories

Reporting area	Reporting Item	Systematic reviews of implantable device by types n (%)					P-value
		Cardiac N=19	Vascular N=124	Orthopedic N=16	Skin grafts N=8	Neurostimulator N=14	
KQ 3							
Validity	Risk of bias was assessed	14 (74)	56 (45)	6 (38)	5 (63)	2 (14)	0.01
	Publication bias was assessed*	11 (73)	45 (45)	3 (43)	0 (0)	0 (0)	0.001
	Quality items or checklists were applied and reported	13 (68)	42 (34)	9 (56)	5 (63)	3 (21)	0.02
Discussion	Study limitations were described	18 (95)	116 (94)	15 (94)	8 (100)	12 (86)	0.89
	Overall strength of the body of evidence was assessed	2 (11)	13 (11)	10 (63)	4 (50)	4 (29)	<0.001
	Future research recommendations were made	14 (74)	100 (81)	13 (81)	8 (100)	13 (93)	0.66
	Funding source was available	12 (63)	53 (43)	3 (19)	2 (25)	5 (36)	0.04
	Authors ties to industry	5 (26)	27 (22)	1 (6)	1 (13)	4 (29)	0.33

* Results were analyzed based on 124 reviews that conducted meta-analyses

Other subgroup analyses

Comparison between reviews by author affiliation to industry

Among 181 eligible systematic reviews, 38 reviews reported that authors conducting systematic reviews had ties to industry, and the remaining 143 reviews did not (Appendix 3 Table 1). Seventy-six reviews (42 percent) identified their funding.

Authors with industry ties were more likely to conduct a meta-analysis than those that did not have industry ties. For all other items, there were no differences across all reporting characteristics between reviews that reported authors' ties to industry and those that did not except for one item of conducting a meta-analysis.

Comparison between reviews that conducted a meta-analysis and that did not

Of the eligible systematic reviews, 124 conducted meta-analyses and the remaining 57 conducted qualitative syntheses. Compared with reviews that conducted meta-analyses, reviews without meta-analyses were less likely to report whether searches were conducted in multiple databases or to look for unpublished data, explicitly report eligibility criteria or eligible studies, handling of heterogeneity, assessment of risk of bias, and specific future research recommendations (Appendix 3 Table 2). Device and operator-specific characteristics across both subgroups were infrequently reported without any differences. Reviews without meta-analyses were more likely to assess overall strength of evidence than reviews that conducted a meta-analysis.

Comparison between reviews by included study designs

Systematic reviews that included observational study designs alone were less likely to identify unpublished data, or to conduct a meta-analysis, or to assess risk of bias. Data on differences within devices were less frequently reported in systematic reviews that included observational studies alone. Similarly, quality items were less frequently reported in systematic reviews that included observational studies alone. However, reviews that included observational studies alone frequently reported specific future research recommendations (Appendix 3 Table 3).

Discussion

The number of systematic reviews of implantable medical devices has grown rapidly in recent years, with reviews being published in a broad range of journals. Our results indicate that current systematic reviews of implantable medical devices generally lack data on the reporting of some important items applicable to any systematic review, as well as data relevant to device- and operator-specific items that are specific to review of implantable medical devices. The device-specific factors—including evolution of technology, generalization of results from one device to a similar device, evaluation of device–operator interactions, and evaluation of team expertise—are important characteristics that should be examined in systematic reviews of implantable medical devices. Since there is no widely accepted guidance for reporting of information unique to implantable medical device studies, failure to report data on procedures and devices could potentially lead to biased synthesis or interpretation of results.

Failure to report the variation in device specifics and operator techniques can potentially confound results. For example, several reviews of stent studies combined sirolimus- and paclitaxel-eluting stents together into a generic category of “drug-eluting stents” when compared to bare-metal stents, without additional subgroup analyses. This highlights a need for the identification and inclusion of items to address device-specific information in a systematic review. The lack of reporting of these potentially important variables may stem from the fact that most reviews focused on evaluating clinical outcomes rather than whether device- or operator-specific variables influenced the clinical outcomes. While this information may have been infrequently reported in the primary studies themselves, it is also possible that the systematic reviews may have simply not noted whether there was reporting of device- or operator-specific data in the primary studies. We cannot comment on the likelihood of this possibility, because we assessed only reviews, not the primary studies.

We identified 30 items from the PRISMA and MOOSE checklists that were relevant to our Key Questions,^{11,12} along with 8 new device-specific and operator-specific items (see final list in Table 1). To our knowledge, there has been no prior empirical evaluation of systematic reviews of implantable medical devices. Although the deficiencies in reporting regarding some of items in systematic reviews of implantable medical devices are similar to those seen in reviews of drug-therapy studies,^{13,14} our findings highlight types of deficiencies that should be remedied. In particular, reviewers should a priori adhere to a specific guideline (e.g., those described in this report) when conducting a systematic review in order to avoid neglecting to report relevant characteristics within primary studies. Secondly, when conducting a review (and transitively, a primary study), it is essential that variation within the intervention with potential to influence or confound outcomes is reported or at least identified and acknowledged as a possible limitation. Consequently, heterogeneity should be adequately evaluated through subgroup or sensitivity analyses.

Our analyses of a large sample of systematic reviews of implantable medical devices found that only 12 of 38 recommended items were commonly reported. Moreover, of the total, 8 items that were unique to the field of medical devices were all infrequently reported. We also identified inadequate reporting of 9 of 17 items that represented the clarity or transparency of methods and results. The quality of reporting varied across device categories. There were no significant differences in quality of reporting when reviews were stratified by authors’ affiliation (vs. nonaffiliation) to industry.

Our review also shows that the majority of the meta-analyses were conducted by applying accepted methodologies (92 percent). The remaining eight percent of the meta-analyses were performed in the presence of great heterogeneity among device groups or among studies combined across designs (e.g., by combining data across study designs of randomized trials and observational studies). In the presence of such heterogeneity, and by combining such studies into meta-analyses, the meaning of the result is unclear. For example, the utility of assessing outcomes of studies confounded by type of drug-eluting stent or performance of different operators at different sites is unclear.

Systematic reviews have gained acceptance as a useful way to summarize data and are also helpful in identifying knowledge gaps within primary studies as well as reviews of those studies. Findings from systematic reviews can help target current and identify future specific research needs. Therefore, good-quality reporting and well-conducted systematic reviews can minimize the likelihood of bias or misinterpretation of results. Systematic reviews and meta-analyses represent a very high level within a hierarchy of evidence, making it all the more important that they are conducted as methodologically rigorous as possible.

Limitations

The quality of reporting within the available primary literature is always a limitation, but these limitations ought to be systematically acknowledged and managed. Some of the generic items were observed to be reported in 100 percent of the reviews, while other items were rarely reported. Our examination relied on reporting by the authors of these reviews. It is possible that the authors of these reviews conducted comprehensive evaluations but were constrained in their reporting owing to journal requirements or the peer-review process. Second, our review relied solely on the reporting of systematic reviews without verification of data from the primary studies included. We did not check for data-extraction errors within the systematic reviews or conduct any reanalysis of primary data from those reviews. Finally, we used liberal inclusion criteria since there is no consensus on the definition of what constitutes a systematic review. By using a very low threshold for reporting of device- and operator-specific information, our results may have inflated the numbers with regard to reporting of these important variables.

Recommendations of reporting items for systematic reviews of implantable medical devices

Reporting of device- or procedure-specific data

Our report identifies that the reporting of study characteristics with regard to device- or procedure-specific data needs to be improved. Differences within devices or across device groups were reported in less than half of the reviews and less than one-tenth of the systematic reviews providing information on operator- or procedure-specific data. It is unclear whether the space allotted or word count of the journal is the reason for this poor reporting; if so, journal editors and reviewers should encourage authors to provide supplementary material for posting on a Web page. Information that should be reported includes the device characteristics, evolution of the device during the study period, details of training or certification of the operator, the operator learning curve, the level of expertise of the operating team or site, variations among practitioners, and volume at the sites that conducted the study.

Herein, we describe a list of device-specific items within each of the five device categories that could be considered in future systematic reviews of implantable medical devices. The items in this list are in no particular order but are limited to those that were described in systematic reviews of implantable devices evaluated in this report.

Cardiac defibrillators with or without pacemakers:

- Device type
- Method of implantation
- Position of the electrode
- Description of microprocessor technology and programmable features
- Alert features that monitor lead impedance

Vascular interventional devices (e.g., stents)

- Type of stent and stenting technique
- Generation of stent (e.g., first or second generation)
- Type of antiproliferative drug used
- Delivery system
- Polymer layer
- Stent frame

Orthopedic implants

- Type of device
- Surgical technique or approach
- Number and location of devices
- Fixation and supplementary materials such as plates and screws
- Type of device coating

Skin-replacement grafts

- Type of skin graft required
- Composition of graft
- Graft type: bioabsorbable or requiring removal

Neurostimulators

- Stimulation parameters
 - frequency

- intensity
- pulse width
- Electrode location

Reporting of generic items as suggested in the PRISMA and the MOOSE statements

Expert panels have identified guidelines for the conduct and reporting of systematic reviews resulting in statements such as the PRISMA and the MOOSE. These statements have been adopted by many major journals as a tool to ensure appropriate conduct and reporting standards for systematic reviews. Journal editors and reviewers should encourage publication of systematic reviews of implantable medical devices that adhere to the conduct and reporting standards as outlined in these statements.

Systematic reviews of implantable devices should clearly state the objective or rationale for conducting a review

We found that the objective or rationale for conducting a systematic review of implantable medical devices was often not stated clearly. A systematic review is often conducted to confirm a result from a primary study, or a meta-analysis may be conducted to increase the sample size and to determine whether the result from a primary study holds in other populations when combined with evidence from other studies. Another objective may be to evaluate sources of heterogeneity. Without stating an objective it is often difficult for readers to understand the exact reason for which a systematic review was conducted or whether the new review would add any new information to existing knowledge base.

Systematic reviews of implantable devices should explicitly report search and study-selection criteria

The majority of reviews of implantable medical devices explicitly reported search criteria and selection of studies. However, only a few conducted searches in languages other than English or attempted to include unpublished data. Moreover, in our review, less than one-half of the reviews reported the numbers of papers identified using a flow diagram, as is suggested in the PRISMA and the MOOSE statements. As compared with published trials, unpublished trials tend to show less beneficial effect, but non-English-language trials and nonindexed trials tend to show larger treatment effects.¹⁵ Therefore, emphasis should be placed on identifying all available evidence by performing a comprehensive literature search (including unpublished studies and non-English-language studies). In addition, comparing unpublished data with published data can be useful in evaluating the potential impact of publication bias.

Systematic reviews of implantable devices should explore heterogeneity through subgroup and sensitivity analyses

Systematic reviews often explore the degree to which data from individual studies (e.g., from sensitivity analyses) or any variation in relation to specific clinical characteristics of the included studies (e.g., from subgroup analyses) affect the main findings. Our report shows that only half of the reviews used subgroup analyses and used sensitivity analyses to test whether the results of their review are robust. Authors usually perform a variety of analyses and they should publish all their analyses.

Systematic reviews of implantable devices should assess the risk of bias of the primary studies included

In our review, only 40 percent of systematic reviews of implantable medical devices assessed the risk of bias or used quality scales or checklists to assess the methodological quality of the primary studies included. Without these assessments, the internal validity of the included primary studies is unknown and therefore the impact of the potential biases in the primary studies on the conclusions of a systematic review remains unclear. Furthermore, transparent reporting of the risk of bias ensures more accurate, less biased summaries of the overall evidence that allow users of the systematic reviews to have a better understanding of the summarized evidence and what biases may exist.

Systematic reviews of implantable devices should list funding sources and authors' conflicts of interest as part of their standard reporting

We found that only 42 percent of systematic reviews reported the funding source, and only about 20 percent reported authors' financial ties to industry. Some empirical evidence from drug-therapy trials has shown an association between the reporting of favorable results and industry funding and financial ties between authors and industry. Systematic reviews of implantable medical devices should, as part of their standard reporting, discuss the potential for bias due to device industry funding and authors' conflicts of interest from financial ties with the device industry.

Systematic reviews of implantable devices should formally assess the overall body of evidence

Only 18 percent of the reviews assessed the overall body of evidence. Rating or evaluating the overall body of evidence allows systematic reviews to link the quality of the overall evidence to the strength of their conclusions. A formal rating system such as the GRADE (Grades of Recommendation Assessment, Development, and Evaluation) allows systematic reviewers to carefully examine the benefits and harms and draw reasoned conclusions by considering the uncertainty of efficacy or effectiveness of an intervention of interest.

Conclusions

We critically appraised 181 systematic reviews of implantable medical devices, most of which were published in recent years. After evaluating these reviews according to the criteria set forth in previous guidelines, we observed that nearly all reviews reported search terms, years of publication searched, inclusion or exclusion criteria, population characteristics at baseline, type of intervention, and types of studies included. Characteristics specific to reviews of implantable medical devices were infrequently reported. These included data on the differences across device characteristics, details of the training or certification of the operator, and the evolution of the device over time. Frequently, meta-analyses were performed in the presence of significant heterogeneity, by combining data across device categories without additional subgroup analyses. Meta-analyses were also performed by combining data across study designs of randomized trials and observational studies.

This review highlights the need for systematic inclusion of items as outlined in the PRISMA and the MOOSE statements when performing any review. In addition, systematic reviews of implantable medical devices need to incorporate device- or operator-specific data, since devices can evolve over time during a study period and can vary appreciably across primary studies. Failure to capture data on procedures and devices could potentially lead to biased synthesis and can potentially impact study results and conclusions.

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- (65) Sakhuja R, Keebler M, Lai TS, McLaughlin GC, Thakur R, Bhatt DL. Meta-analysis of mortality in dialysis patients with an implantable cardioverter defibrillator. *Am J Cardiol*. 2009;103:735-741.PM:19231344 (*Reject reason: Duplicate retrieval*)
- (66) Oswald H, Klein G, Struber M, Gardiwal A. Implantable defibrillator with left ventricular assist device compatibility. *Interact Cardiovasc Thorac Surg*. 2009;8:579-580.PM:19223309 (*Reject reason: Primary study*)
- (67) Mandava P, Kent TA. Percutaneous clot removal in acute ischemic stroke. *Arch Neurol*. 2009;66:283-284.PM:19204174 (*Reject reason: Commentary*)
- (68) Naylor AR. Does the risk of post-CABG stroke merit staged or synchronous reconstruction in patients with symptomatic or asymptomatic carotid disease? *J Cardiovasc Surg (Torino)*. 2009;50:71-81.PM:19179993 (*Reject reason: Not a systematic review*)
- (69) Amin AP, Mamtani MR, Kulkarni H. Factors influencing the benefit of adjunctive devices during percutaneous coronary intervention in ST-segment elevation myocardial infarction: meta-analysis and meta-regression. *J Interv Cardiol*. 2009;22:49-60.PM:19141090 (*Reject reason: Intervention not of interest*)
- (70) Takkenberg JJ, Klieverik LM, Schoof PH et al. The Ross procedure: a systematic review and meta-analysis. *Circulation*. 2009;119:222-228.PM:19118260 (*Reject reason: Evaluation of autograft*)
- (71) Jolly SS, Amlani S, Hamon M, Yusuf S, Mehta SR. Radial versus femoral access for coronary angiography or intervention and the impact on major bleeding and ischemic events: a

- systematic review and meta-analysis of randomized trials. *Am Heart J.* 2009;157:132-140.PM:19081409 (*Reject reason: Topic not of interest*)
- (72) Sleilaty G, Achouh P, Fabiani JN. [Stenting or coronary artery bypass surgery for triple vessel disease?]. *Ann Cardiol Angeiol (Paris).* 2009;58:104-112.PM:18930176 (*Reject reason: Not a systematic review*)
- (73) Patel TR, Bulsara KR. Current strategies for the treatment of intracranial atherosclerotic internal carotid artery stenosis. *Neurosurg Rev.* 2009;32:23-27.PM:18818960 (*Reject reason: Narrative review*)
- (74) Hanson MD, Gauld M, Wathen CN, Macmillan HL. Nonpharmacological interventions for acute wound care distress in pediatric patients with burn injury: a systematic review. *J Burn Care Res.* 2008;29:730-741.PM:18695617 (*Reject reason: Intervention not of interest*)
- (75) De LG, Cassetti E, Marino P. Impact of duration of clopidogrel prescription on outcome of DES as compared to BMS in primary angioplasty: a meta-regression analysis of randomized trials. *J Thromb Thrombolysis.* 2009;27:365-378.PM:18498003 (*Reject reason: Intervention not of interest*)
- (76) Tomaske M, Bauersfeld U. Experience with implantable cardioverter-defibrillator therapy in grown-ups with congenital heart disease. *Pacing Clin Electrophysiol.* 2008;31 Suppl 1:S35-S37.PM:18226033 (*Reject reason: Narrative review*)
- (77) Celik T, Iyisoy A, Yuksel UC, Isik E. Optimal revascularization strategy for diabetic patients with multivessel coronary artery disease: the duel between old hero and young warrior. *Int J Cardiol.* 2009;131:269-270.PM:17692947 (*Reject reason: Editorial*)
- (78) Bryant J, Brodin H, Loveman E, Payne E, Clegg A. The clinical and cost-effectiveness of implantable cardioverter defibrillators: a systematic review. *Health Technol Assess.* 2005;9:1-150, iii.PM:16153353 (*Reject reason: Duplication publication*)
- (79) Pourati I, Hyder M, Rosenthal L. Indications for implantable cardiac defibrillators in patients with congestive heart failure: implications of the sudden cardiac death in heart failure trial. *Curr Cardiol Rep.* 2005;7:223-228.PM:15865865 (*Reject reason: Narrative review*)

(80) Nanthakumar K, Epstein AE, Kay GN, Plumb VJ, Lee DS. Prophylactic implantable cardioverter-defibrillator therapy in patients with left ventricular systolic dysfunction: a pooled analysis of 10 primary prevention trials. *J Am Coll Cardiol.* 2004;44:2166-2172.PM:15582314

(Reject reason: Met sufficient number of reviews)

(81) Seidl K, Strauss M, Kleemann T. [ICD therapy as secondary prevention].

Herzschrittmacherther Elektrophysiol. 2010;21:96-101.PM:20505945 *(Reject reason: Narrative review)*

Appendix 1. Search Strategy

1 defibrillators, implantable/ or pacemaker, artificial/ or cardiac resynchronization therapy devices/ or heart, artificial/ or heart-assist devices/ or Heart Valve Prosthesis/ (26457)

2 (defibrillator* or pacemaker* or cardiac resynchronization therapy device* or artificial heart or heart assist device* or heart valve prosth*).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] (42310)

3 implantable neurostimulators/ or neural prostheses/ or auditory brain stem implants/ or cochlear implants/ or Deep Brain Stimulation/ (5661)

4 (neurostimulat* or neural prosthe* or brain stem implant* or cochlear implant* or deep brain stimulat*).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] (10382)

5 "prostheses and implants"/ or absorbable implants/ or artificial limbs/ or bioprosthesis/ or orthopedic fixation devices/ or external fixators/ or internal fixators/ (28244)

6 (artificial limb* or bioprosth* or orthopedic fixation device* or external fixator* or internal fixator*).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] (13888)

7 blood vessel prosthesis/ or stents/ or drug-eluting stents/ (40837)

8 (blood vessel prosthe* or stent* or drug-eluting stent*).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] (57375)

9 (skin graft* or wound care or skin replac*).mp. or Skin, Artificial/ [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] (9349)

10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (142446)

11 meta-analysis.pt. (24009)

12 meta-analysis.sh. (24009)

13 (meta-analys\$ or meta analys\$ or metaanalys\$).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] (43475)

14 (systematic\$ adj9 review\$).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] (29696)

15 (systematic\$ adj9 overview\$).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] (615)

16 (quantitativ\$ adj9 review\$).mp. (2098)

17 (quantitativ\$ adj9 overview\$).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] (161)

18 (quantitativ\$ adj9 synthesis\$).mp. (907)

19 (methodologic\$ adj9 review\$).mp. (3153)

20 (methodologic\$ adj9 overview\$).mp. (173)

21 (integrative research review\$ or research integration).mp. (48)

22 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 (67875)

23 10 and 22 (1385)

24 limit 23 to yr="2009 - 2010" (467)

Appendix 2. Data Extraction Form

Timestamp

Author Year PMID

Extractor initials

Was the funding source declared?

Do the authors have industry ties?

Objective elements of PICO stated?

Study Design(s) Included

Search Terms Included in Full-text?

>1 database searched?

Search Year Start

Search Year End

Searched in >1 Language?

Searched grey literature?

Study Flow Diagram Included?

Number of Excluded full-texts given?

Inclusion criteria given?

Reason(s) for exclusions given?

Data extraction checked, or method described?

Total number of included full-texts in SR:

Any meta-analysis performed?

If meta-analysis/es performed, how many unique studies included in MA in total?

Describe the patient population

Intervention/exposure

Comparator

Type(s) of outcomes

Is control group defined as Standard of Care or Optimized Care?

Adverse events reported?

If adverse events reported, length of follow up is:

Was there heterogeneity in follow-up times across studies?

Was there any discussion or evaluation at procedural and/or device level?

Data on differences across device characteristics available or discussed?

Data on differences within device characteristics available or discussed?

Were the evolution of devices over time discussed?

Other descriptions of device characteristics

Any details included on background experience of implant team or surgeon?

Training/certification of provider reported?

Ramp-up in provider technique (ie learning curve) discussed?

Level of expertise of team/site considered when full-texts were evaluated?

Practitioner variability discussed?

* Industry support?

* Employed by Industry?

* Efficacy

* Safety

* < 2 years

* ≥ 2 years

"Volume at sites" effect discussed?

At least one subgroup analysis considered?

If subgroup analysis/es considered, quantified?

Was a meta-analysis performed?

If meta-analysis performed, was accepted methodology used?

If meta-analysis performed, what model(s) was used?

Which of the following were reported?

Was there a quantitative assessment for heterogeneity in at least one of the meta-analyses?

Was there an assessment for risk of bias?

Graphical representation of results?

Was a sensitivity analysis proposed? (Methods)

Reporting of concurrent / co-medications in the study population?

Was there heterogeneity within each device group?

If there was heterogeneity within each device group, was it analyzed?

Were studies grouped according to study design?

Cost-effectiveness discussed?

Future research recommendations made?

Specific quality checklist used?

Was an overall rating for the body of evidence given?

Were the results of a sensitivity analysis reported or discussed?

What are some of the limitations of the primary studies identified in the review?

By outcome, which treatment is favored?

General notes or comments

Category of device

- * Simple summary data for each group
- * Effect estimates
- * Confidence intervals
- * I^2
- * Forest plot
- * Other

Appendix 3 Tables 1-3 Subgroup analyses

Appendix 3 Table 1. Reporting of characteristics in systematic reviews of implantable medical devices according to reported author affiliation.

Reporting area	Reporting Item	Systematic reviews n (%)			Total n (%)
		Authors ties to industry N=38	No ties to Industry reported N=143	P-value	
KQ1					
Search	Search terms were described or referred to elsewhere	33 (87)	132 (92)	0.36	165 (91)
	Multiple databases were searched	30 (79)	114 (79)	1.0	144 (79)
	Years searched were described	33 (87)	129 (90)	0.57	162 (89)
	Multiple languages were included in search	9 (24)	53 (37)	0.18	62 (34)
	Authors explicitly stated searching for unpublished data	17 (44)	63 (44)	1.0	80 (44)
Selection	Inclusion or exclusion criteria were stated	37 (97)	138 (96)	1.00	175 (96)
	Population at baseline was reported	38 (100)	143 (100)	NA	181 (100)
	Interventions/exposures were described	38 (100)	143 (100)	NA	181 (100)
	Comparators were described	38 (100)	141 (98)	1.0	152 (84)
	Outcomes were described	38 (100)	143 (100)	NA	154 (85)
	Types of studies included were reported	37 (97)	138 (96)	1.00	175 (96)
	Number of studies included and excluded were reported	37 (97)	141 (98)	1.0	116 (61)
Reasons for exclusion were described	30 (79)	109 (76)	0.83	139 (76)	
Results	A flow diagram for the number of studies included and excluded was used	20 (53)	60 (42)	0.27	80 (44)
	Results were presented graphically	29 (76)	88 (61)	0.09	117 (64)
	Meta-analyses were performed	32 (84)	92 (64)	0.02	124 (68)
	Costs or cost-effectiveness were described	5 (13)	37 (26)	0.13	42 (23)
KQ2					
Device-specific Variables	Data on differences across device characteristics were discussed	16 (42)	70 (49)	0.58	86 (47)
	Data on differences within device characteristics were available	14 (37)	51 (35)	0.85	65 (36)
	Evolution of devices over time were discussed	6 (16)	26 (18)	1.0	32 (18)

Continued..

Appendix 3 Table 1 . Continued

Reporting area	Reporting items	Systematic reviews of study types			Total n (%) N=181
		Authors ties to industry N=38	No ties to Industry reported N=143	P-value	
KQ 2 continued					
Operator-specific Variables	Details of training/certification of provider were reported	2 (5)	0 (0)	0.04	2 (1)
	Ramp-up in provider technique (i.e. learning curve) was discussed	2 (5)	11 (8)	1.0	13 (7)
	Level of expertise of team/site were considered	2 (5)	14 (10)	0.53	16 (9)
	Practitioner variability were discussed	5 (13)	13 (9)	0.54	18 (10)
	"Volume at sites" effect were discussed	3 (8)	11 (8)	1.0	14 (8)
Handling of heterogeneity	Models for meta-analyses were reported	37 (97)	86 (70)	0.50	123 (99)
	Meta-analyses used accepted methodologies (e.g. studies grouped by design)	27 (71)	87 (60)	0.35	114 (62)
	Heterogeneity was assessed or discussed?	32 (84)	107 (74)	0.28	139 (76)
	Sensitivity analyses were assessed or discussed	14 (37)	51 (35)	0.85	65 (36)
	Results by subgroups were considered or quantified	11 (29)	29 (20)	0.27	40 (22)
KQ3					
Validity	Risk of bias was assessed	17 (45)	62 (43)	0.85	79 (43)
	Publication bias was assessed	13 (34)	46 (32)	0.85	59 (48)
	Quality items or checklists were applied and reported	14 (37)	58 (40)	0.85	72 (40)
Discussion	Study limitations were described	37 (97)	138 (96)	1.0	175 (96)
	Overall strength of the body of evidence was assessed	5 (13)	28 (19)	0.48	33 (18)
	Specific future research recommendations were made	30 (79)	119 (83)	0.64	149 (82)
	Funding source was identified	20 (53)	56 (39)	0.14	76 (42)

Appendix 3 Table 2. Reporting characteristics in systematic reviews (with or without meta-analyses) of implantable medical devices

Topic	Reporting Item	Systematic reviews with and without meta-analyses			Total n (%) N=181
		Meta-analysis N=124	No meta-analyses N=57	P-value	
KQ1					
Search	Search terms were described or referred to elsewhere	115 (92)	50 (88)	0.41	165 (91)
	Multiple databases were searched	105 (84)	39 (68)	0.02	144 (79)
	Years searched were described	113 (91)	49 (84)	0.21	162 (89)
	Multiple languages were included in search	48 (38)	14 (25)	0.09	62 (34)
	Authors explicitly stated searching for unpublished data	66 (53)	14 (25)	<0.001	80 (44)
Selection	Inclusion or exclusion criteria were stated	122 (98)	53 (91)	0.03	175 (96)
	Population at baseline was reported	124 (100)	57 (100)	NA	181 (100)
	Interventions/exposures were described	124 (100)	57 (100)	NA	181 (100)
	Comparators were described	123 (99)	56 (99)	0.24	152 (84)
	Outcomes were described	110 (88)	44 (77)	0.08	154 (85)
	Types of studies included were reported	121 (98)	55 (95)		176 (96)
	Number of studies included and excluded were reported	91 (73)	25 (44)	<0.001	116 (61)
Reasons for exclusion were described	105 (85)	34 (59)	<0.001	139 (76)	
Results	A flow diagram for the number of studies included and excluded was used	66 (53)	14 (25)	<0.001	80 (44)
	The total number of primary studies included in the systematic review/meta-analysis was reported	2876	1419	NA	182
	Results were presented graphically	114 (91)	3 (5)	<0.001	117 (64)
	Costs or cost-effectiveness were described	24 (19)	18 (32)	0.09	42(23)
KQ2					
Device-specific Variables	Data on differences across device characteristics were discussed	61 (49)	25 (44)	0.63	86 (47)
	Data on differences within device characteristics were available	48 (38)	17 (30)	0.32	65 (36)
	Evolution of devices over time were discussed	23 (18)	15 (26)	0.24	38 (21)

Continued..

Appendix 3 Table 2. Continued

Topic	Quality Criteria	Systematic reviews with and without meta-analyses			Total n (%) N=181
		Meta-analysis N=124	n (%) No meta-analyses N=57	P-value	
KQ 2 continued					
Operator-specific Variables	Details of training/certification of provider were reported	2 (2)	0 (0)	0.47	2 (1)
	Ramp-up in provider technique (i.e. learning curve) was discussed	9 (7)	4 (7)	0.62	13 (7)
	Level of expertise of team/site were considered	10 (8)	6 (11)	0.58	16 (9)
	Practitioner variability were discussed	13 (11)	5 (9)	0.50	18 (10)
	"Volume at sites" effect were discussed	7 (6)	7 (12)	0.14	14 (8)
Handling of heterogeneity	Models for meta-analyses were reported	121 (97)	NA	NA	123 (99) ^a
	Meta-analyses used accepted methodologies (e.g. studies grouped by design)	114 (92)	NA	NA	114 (62) ^a
	Heterogeneity was assessed or discussed?	112 (90)	27 (48)	<0.001	139 (76)
	Sensitivity analyses were assessed or discussed	60 (48)	5 (9)	<0.001	65 (36)
	Results by subgroups were considered or quantified	77 (62)	15 (26)	<0.001	92 (51)
KQ3					
Validity	Risk of bias was assessed	71 (57)	8 (14)	<0.001	79 (43)
	Publication bias was assessed	59 (46)	NA	NA	59 (46) ^a
	Quality items or checklists were applied and reported	53 (43)	19 (33)	0.26	72 (40)
Discussion	Study limitations were described	56 (97)	119 (96)	1.0	175 (96)
	Overall strength of the body of evidence was assessed	14 (11)	19 (33)	0.001	33 (18)
	Specific future research recommendations were made	96 (77)	53 (93)	0.007	149 (82)
	Funding source was identified	57 (42)	19 (33)	0.15	76 (42)
	Author ties to industry was reported	32 (26)	6 (10)	0.03	38 (21)

a. Among 182 eligible systematic reviews, 124 conducted a meta-analysis. One of 124 studies did not report a model for meta-analysis

Appendix 3 Table 3. Reporting characteristics in systematic reviews of implantable medical devices by study types

Topic	Reporting Item	Systematic reviews by study types n (%)			P-value
		Intervention N=66	Observational N=51	Both N=64	
KQ1					
Search	Search terms were described or referred to elsewhere	58 (88)	48 (94)	59 (92)	0.59
	Multiple databases were searched	57 (86)	32 (63)	55 (86)	0.005
	Years searched were described	60 (91)	44 (86)	58 (90)	0.76
	Multiple languages were included in search	31 (47)	11 (22)	20 (31)	0.01
	Authors explicitly stated searching for unpublished data	43 (65)	15 (29)	22 (34)	<0.001
Selection	Inclusion or exclusion criteria were stated	63 (96)	50 (98)	62 (97)	0.79
	Population at baseline was reported	66 (100)	51 (100)	64 (100)	NA
	Interventions/exposures were described	66 (100)	51 (100)	64 (100)	NA
	Comparators were described	66 (100)	49 (96)	64 (99)	0.20
	Outcomes were described	66 (100)	51 (100)	64 (100)	NA
	Number of studies included and excluded were reported	63 (96)	51 (100)	64 (100)	0.46
Results	Reasons for exclusion were described	48 (73)	39 (77)	52 (80)	0.61
	A flow diagram for the number of studies included and excluded was used	31 (47)	18 (35)	31 (48)	0.36
	Results were presented graphically	58 (88)	21 (41)	38 (58)	<0.001
	Costs or cost-effectiveness were described	17 (26)	6 (12)	19 (29)	0.06
	Meta-analyses were performed	59 (89)	23 (45)	42 (64)	<0.001
KQ2					
Device-specific Variables	Data on differences across device characteristics were discussed	29 (44)	23 (45)	34 (55)	0.60
	Data on differences within device characteristics were available	32 (48)	11 (22)	22 (34)	0.01
	Evolution of devices over time were discussed	12 (18)	11 (22)	15 (23)	0.76

Continued..

Appendix 3 Table 3. Continued

Topic	Quality Criteria	Systematic reviews of study types n (%)			P-value
		Intervention N=66	Observational N=51	Both N=64	
KQ 2 continued					
Operator-specific Variables	Details of training/certification of provider were reported	1 (2)	0 (0)	1 (2)	1.0
	Ramp-up in provider technique (i.e. learning curve) was discussed	3 (5)	6 (12)	4 (6)	0.31
	Level of expertise of team/site were considered	3 (5)	7 (14)	6 (9)	0.20
	Practitioner variability were discussed	6 (9)	6 (12)	6 (9)	0.86
	"Volume at sites" effect were discussed	2 (3)	6 (12)	6 (9)	0.15
Handling of heterogeneity	Models for meta-analyses were reported	65 (99)	50 (98)	64 (100)	1.00
	Meta-analyses used accepted methodologies (e.g. studies grouped by design)	59 (89)	20 (39)	36 (56)	<0.001
	Heterogeneity was assessed or discussed?	42 (63)	24 (47)	37 (57)	0.20
	Sensitivity analyses were assessed	32 (48)	10 (20)	23 (35)	0.005
	Results by subgroups were considered or quantified	19 (29)	8 (16)	13 (20)	0.22
KQ3					
Validity	Risk of bias was assessed	39 (59)	15 (29)	25 (36)	0.003
	Publication bias was assessed	34 (52)	8 (16)	17 (26)	<0.001
	Quality items or checklists were applied and reported	33 (50)	12 (23)	27 (42)	0.01
Discussion	Study limitations were described	63 (96)	50 (98)	62 (97)	0.79
	Overall strength of the body of evidence was assessed	10 (15)	10 (19)	13 (20)	0.79
	Specific future research recommendations were made	48 (73)	47 (92)	54 (84)	0.03
	Funding source was declared	33 (50)	22 (43)	21 (32)	0.12
	Authors with ties to industry was reported	16 (24)	8 (16)	14 (22)	0.55