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MEDICAL DEVICES EARLY ASSESSMENT METHODS: SYSTEMATIC LITERATURE REVIEW

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Objectives: The aim of this study was to get an overview of current theory and practice in early assessments of medical devices, and to identify aims and uses of early assessment methods used in practice.
Methods: A systematic literature review was conducted in September 2013, using computerized databases (PubMed, Science Direct, and Scopus), and references list search. Selected articles were categorized based on their type, objective, and main target audience. The methods used in the application studies were extracted and mapped throughout the early stages of development and for their particular aims.
Results: Of 1,961 articles identified, eighty-three studies passed the inclusion criteria, and thirty were included by searching reference lists. There were thirty-one theoretical papers, and eighty-two application papers included. Most studies investigated potential applications/possible improvement of medical devices, developed early assessment framework or included stakeholder perspective in early development stages. Among multiple qualitative and quantitative methods identified, only few were used more than once. The methods aim to inform strategic considerations (e.g., literature review), economic evaluation (e.g., cost-effectiveness analysis), and clinical effectiveness (e.g., clinical trials). Medical devices were often in the prototype product development stage, and the results were usually aimed at informing manufacturers.
Conclusions: This study showed converging aims yet widely diverging methods for early assessment during medical device development. For early assessment to become an integral part of activities in the development of medical devices, methods need to be clarified and standardized, and the aims and value of assessment itself must be demonstrated to the main stakeholders for assuring effective and efficient medical device development.

Keywords: Health technology assessment, Medical devices, Healthcare economics and organizations, Cost-effectiveness, Translational research

Each year a huge number of medical devices are being developed, but only a few make it to the market (1). The development process of medical devices is a costly and uncertain undertaking. Failed development does not only result in lack in economic return for the company, but also in high costs without healthcare improvements for society (1–3). There are multiple reasons for failed device development, but one important factor is the late evaluation of the potential of the device in healthcare practice, usually only after the prototype design is finalized. Various authors suggested that assessment of medical devices early in the development process, at the stage where it is still possible to curtail the diffusion or influence their development in simple and inexpensive manner, may be beneficial (1;4–7).

Based on the health technology assessment (HTA) definition of the International Network of Agencies for Health Technology Assessment "early assessment of medical devices" can be defined as the early examination of the medical, economic, social, and ethical implications of the medical device to determine the potential for incremental value in healthcare (8). It starts from initial idea generation up to stage I of clinical trials (Figure 1) (9–12). At each of the stages, different qualitative and quantitative assessment methods can be used, to provide information that is of interest in that stage to feed the decision-making process of the responsible stakeholders (10).

At present, most of the decisions made early in development seem to be taken quickly and in the absence of good quality evidence, although those decisions can have a long-term impact on device design (21). Early phases of development are characterized by manufacturers enthusiasm, competition, and desire to pioneer, which can result in false judgment based information which relies on insufficient information (13). Early assessment of the medical device in the healthcare context could help to support and guide decisions with as much evidence or motivated assumptions as possible (14).

The aim of early assessment is to reduce the failure rate at each stage of the development process, while enhancing the efficiency of R&D and of limited resources use, through prioritization of the innovations most likely to succeed among others. It may also be used to support reimbursement claims by providing quantitative input for developing risk-sharing agreements (2;3;11;15;16).

Several studies have indicated the importance of on-going assessment as an integral part of the medical devices development process (3;14;17;18), but there is still lack of general understanding on which methods should be used at the different stages, which data should be gathered to inform early decision

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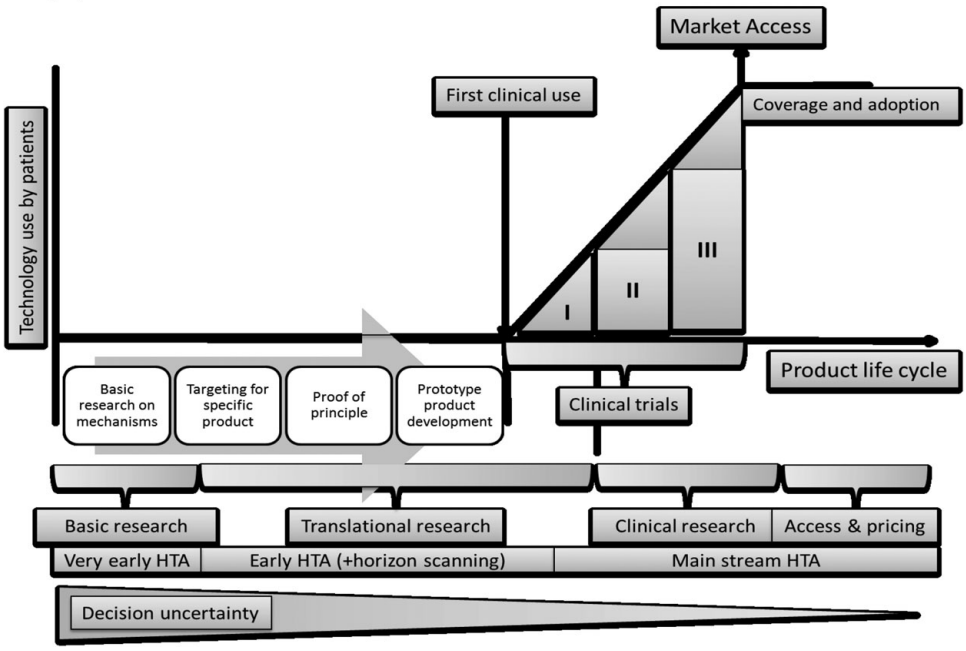

Figure 1. A simplified flow-chart of stages in medical product development based on IJzerman and Steuten, 2011 [10].

making, as well as how to use the results to inform stakeholders. The overall aim of this study is to describe the current state of the art in early assessment and to identify assessment methods that help to inform decisions during the development stage of medical devices, so that medical devices are less likely to be market failures and more likely to be approved by regulatory and reimbursement agencies. This implicit aim is important and has not been previously answered.

METHODS

Searching for Relevant Studies

A systematic literature review was performed to identify studies reporting on early assessment to help inform the early development of medical devices. The first objective was to select theoretical and application papers reporting on early assessments of medical devices. The second objective was to identify the assessment methods in use and map their use throughout the aims and stages of early development.

A systematic search strategy was conducted in September 2013 using (i) computerized databases (PubMed, Science Direct, and Scopus) and (ii) reference search of included articles. Search strategies were built based on the keywords, such as technolog*, approval, biomedical, design, early HTA, equipment, assessment, medical development, model*, device, valu*, healthcare, R&D, strategic plan*, innovat*, cost*, health, project management, decision mak*, and medical subject headings (MeSH): Technology assessment, biomedical; Biomedical technology; Technology, high cost; Device approval; Equipment design; Technology transfer. Supplementary Table 1, which can be viewed online at http://dx.doi.org/10.1017/S0266462314000026, provides a detailed overview of the search strategies and their results. Furthermore, reference lists of included papers were hand searched.

Selection Criteria for All Studies

The selection was restricted to articles in English, involving human subjects and published after 1996, as the growing interest in methods that more specifically inform decisions in earlier stages of product development is a fairly recent trend. Only full journal articles and papers with ISBN and ISSN numbers were included in the review. The review of the articles was accomplished in two consecutive screenings. In the first screening, the titles and abstracts were reviewed for relevance by two authors (K.M. and J.v.T.) according to the following inclusion criteria: (i) the articles written within the healthcare context; and (ii) articles reporting on theory or practice of assessment of a medical technology. Relevant articles were obtained as a full text and assessed against the selection criteria (K.M. and J.v.T.). Disagreements were resolved by discussion or referred to a third author (M.I.J.). Articles eligible for the review were chosen after the careful reading of the full article. In this stages, articles were excluded if they did not report on early assessment (as defined below) of medical devices.

Based on the definition provided by the U.S. Food and Drug Administration a "medical device" was defined as an instrument, apparatus, implant, in vitro reagent, or similar or related article that is used to diagnose, prevent, or treat disease or other conditions, and does not achieve its purposes through chemical action within or on the body. "Early assessment of medical device" was defined as the assessment of the value of medical device under development at the time when investments and

design decisions have to be made with high uncertainties about future prospects, up to stage I of clinical trials (when the design is mostly finalized and the device is not yet implemented). Because of the broad nature of the study aims and the wide variety of studies applying different methods that were included, no quality instrument was available for the authors to use.

Categorization of the Papers

All articles selected for the review were categorized as "theoretical papers," which aimed at building a framework for early assessment (including systematic reviews of existing literature) or "application papers," which are case studies of early assessment, or illustrations of theory using examples.

Data Extraction and Synthesis

From each paper, the study objectives and assessment methods were identified and grouped based on common aims. The study objectives were next classified for specific target audience they aimed to inform, and the assessment methods were classified based on the early stage of medical device development they were used at. Additionally, the methods used in the application papers were identified and classified into either qualitative or quantitative. The following outcomes were extracted:

Main target audience: Decision makers on coverage and reimbursement; policy makers; manufacturers; varied. The main target audience was determined based on the early assessment decision support system presented by Pietzsch and Paté-Cornell (19).

Device development stage: Basic research on mechanisms; targeting for specific product; proof of concept; prototype product development; first clinical trials; not specified. The development stages were determined based on the simplified framework presented in Figure 1.

Study objectives and early assessment methods: Not prespecified but categorized on the basis of the data obtained.

Categorization of the outcome variables was based upon the agreement between the authors.

RESULTS

Literature Search Strategy

Figure 2 presents a flow chart of the literature selection procedure. The systematic literature search yielded 1,961 hits. Eighty-three articles immediately met the inclusion criteria and were selected from the search strategy. Another thirty articles were selected based on screening of the references in the selected articles. Eighty-two of the 113 selected studies were application papers, and thirty-one studies were theoretical papers.

Early Assessment Objectives in Theory and in Practice

Table 1 presents the study objectives of selected articles, which are categorized according to their main target audience, and subdivided to theoretical and applications papers.

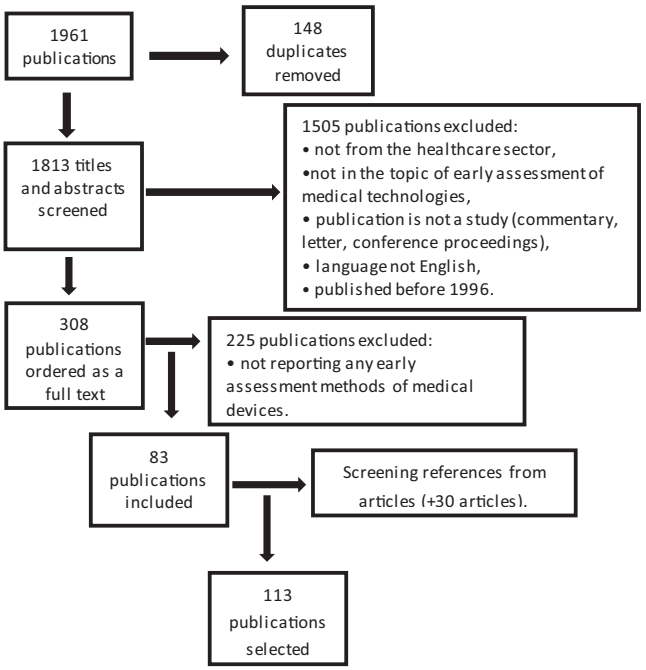

Figure 2. Flow chart: selection of the literature.

From the analysis (Table 1), it became apparent that the main target audience for early assessment are the manufacturers. Most application papers reported on the potential applications or improvement directions for a medical devices, in some cases in a specific disease context (thirty articles). Although it was decided that these papers mainly targeted manufacturers, who scan the emerging trends and developments in the targeted disease area for new insights to develop strategies for anticipating future developments (88–117), they could as well be addressed to the policy makers, who based on them decide on the societal funds. The analysis also revealed that there is a focus on developing a framework for early assessment of medical device (twenty articles). Some frameworks propose to support decision-making processes in medical device development through analytical decision support techniques (9;10;13;18;62;66;70;72;73), while others address the specific demands of the early development context (74–76). A third important aim in early assessment is to include end-user perspectives in further development of a medical device (eighteen articles). These studies aim to convince manufacturers of the value of end-user perspective on development (49–52;55;59), mainly through giving practical examples. Five studies focus on the theoretical development of this study area (44;45;47;48;60).

Systematic Analysis of Early Assessment Methods in Use

Table 2 presents different qualitative and quantitative methods used in the application papers at different stages of early development of medical devices grouped according to their aims. Supplementary Table 2, which can be viewed online at

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Table 1. Study Objectives in Selected Articles According to Addressed Main Target Audience

	Decision makers on coverage and reimbursement		Policy makers		Manufacturers		Varied	
Main target audience/Study objective	T	P	T	P	T	P	T	P
To assess the clinical value of a medical device early in development		[20]; [21]; [22]; [23]; [24]			[25];[26];	[11]; [27]; [28]; [29]; [30]		
To assess the economic value of a medical device early in development		[31]; [32]		[33]		[12]; [34]; [35]; [36]		
To develop the methods for cost-effectiveness analysis early in medical device development	[17]; [37]; [38]			[16]	[39];[14]	[3]	[40]	[41]
To assess investments required in further development of a medical device		[42]; [43]				[15]		
To include stakeholder perspectives in further development of a medical device	[44]	[45]; [46]			[47]; [48]	[49]; [50]; [51]; [52]; [53]; [54]; [55]; [56]; [57]; [58]; [59]	[60]	[61]
To propose or develop a framework (i.e. sequence of methods to assess different aspects of technology) for early assessment of medical device	[62]	[13]; [63]; [64]; [65]	[10]	[18]; [66]	[67]; [68]; [69]	[9]; [70]; [71]; [19]; [72]	[73]; [74]; [75]	[76]
To propose/analyse a method for the early identification/assessment of a medical device	[77]		[78]; [79]; [80]; [81]	[82]	[83];		[84]	[85]
To investigate potential applications or improvement directions for (a) medical device(s) and/or the potential of medical devices in a specific disease area.	[86]	[87]				[88]; [89]; [90]; [91]; [92]; [93]; [94]; [95]; [96]; [97]; [98]; [99]; [100]; [101]; [102]; [103]; [104]; [105]; [106]; [107]; [108]; [109]; [110]; [111]; [112]; [113]; [114]; [115]; [116]; [117];	[118]	[119]

T, theoretical papers (incl. systematic reviews); P, application papers [incl. theoretical papers with example].

Table 2. Quantitative and Qualitative Methods Used in the Early Assessment of Medical Devices According to the Stage of Development and Their Aims

Methods aim/ Stage of development	Strategic analysis (incl. stakeholder analysis)	Economic evaluation	Clinical effectiveness
Basic research on mechanisms	1; 2;		
Targeting for specific product	1; 3; 4; 5; 6; 7; 8; 22;	I;	
Proof of concept	1; 5;	II; III; XVII;	
Prototype product development	1; 4; 5; 8; 9; 10; 11; 12; 14; 20; 24; VIII; IX; XI; XIII; XIX;	I; II; IV; V; VI; VII; X;	25;
First clinical trials	1; 10; 12; 13; XIII; XV;	II; III; XII; XIV;	21;
Not specified	1;4; 5; 7; 10; 12; 14; 15; 16; 17; 18; 19; 20; 23; IX; XV; XVI; XVIII;	I; II; III;V; XIV; XVII;	

Note. Qualitative methods used in the early assessment of medical devices: Literature review/analysis (e.g. archives, documents) [1]; Peer review [2]; User profiles building [3]; Focus groups [4]; Interviews (e.g. experts) [5]; Informal discussions [6]; Qualitative weighing of relevant factors [7]; Use cases writing [8]; Key informant interviews [9]; Strategic planning methods: PEST, SWOT [10]; Soft Systems Methodology [11]; Expert panels/elicitation [12]; Technology profiling (uncertainty profile and evidence profile) [13]; Workshops [14]; Surveys [15]; R&D portfolio management [16]; Brainstorming sessions [17]; Users-producers seminars [18]; Usability tests [19]; Users feedbacks [20]; Clinical trials [21]; Choice-based conjoint analysis (Discrete choice modelling) [22]; Horizon scanning [23]; Preliminary market research [24]; Bench studies [25].
Quantitative methods used in the early assessment of medical devices: Headroom analysis [I]; Cost-effectiveness analysis (CEA) [II]; Probabilistic sensitivity analysis (PSA) [III]; Potential years of life lost (PYLL) [IV]; Cost-benefit analysis (CBA) [V]; Cost-utility analysis (CUA) [VI], Opportunity costs (used as indicators to which relative weights are assigned) [VII]; Roadmapping process (Multi-Path Mapping) [VIII]; Scenarios building [IX]; Return on investment [X]; Technological forecasting based on epidemiological data [XI]; Rudimental analysis of costs [XII]; MultiCriteria Decision Analysis (Analytic Hierarchy Process) [XIII]; VOI Expected Value of Perfect Information (EVPI) [XIV]; Bayesian modelling/statistics (data pooling, random effects analysis) [XV]; Probabilistic Risk Analysis [XVI]; Real options analysis [XVII]; Best-worst scaling (BWS) [XVIII]; Decision tree analysis [XIX].

http://dx.doi.org/10.1017/S0266462314000026, presents definitions and objectives of those methods.

Most of the application papers do not specify the stage of device development of the device or they reported that the early assessment took place in the prototype product development phase. There is great diversity in the methods used in early assessment and in their goals. Early assessment comprises a strategic analysis (including stakeholders analysis) of the medical context and the competition, evaluation of the economic impact of medical devices and early assessment of clinical effectiveness of the medical devices under development, all with the aim to reduce uncertainty in the developmental stage of a medical device. Qualitative and quantitative research methods are about equally applied in the different stages of medical device development, but do differ based on aims.

Main Objectives of Early Assessment

Strategic Considerations. A large focus in early assessment is on strategic considerations. In assessing strategic issues that could influence development, two methods of study can be distinguished: literature review and stakeholder involvement. Desk search analysis is usually performed to analyze the market/knowledge gaps and potential applications for medical devices under development, through literature review/analysis (9;13;29;49;59), SWOT (Strengths, Weaknesses, Opportunities, and Threats analysis), or PEST (Political, Economic, Social, and Technological analysis) analysis (9;15) and/or horizon scanning (45;78;82;119). The aims of stakeholder involvement, stakeholder analysis (49–57) is thought to increase understanding of needs and wants of policy makers and end users to tailor their device to the health context (58;120). Main methods used for stakeholder involvement are focus groups, interviews, expert panels, workshops, or surveys (15;33;52;54;57;59;121). The great majority of studies were qualitative in nature, although in some cases ranking or rating of factors took place. One of the more often used quantitative methods was a Bayesian modeling/statistics, which is based on modeling of the evidence about the true state of the world expressed in terms of degrees of belief, and scenarios building—a creative method for trend extrapolation and envision of alternative paths into the future.

Economic Evaluations. Economic evaluation is in its nature a quantitative methods. Cost-effectiveness analysis (CEA) with subsequent probabilistic sensitivity analysis (PSA) was performed starting with the proof of concept stage of the development. An interesting new technique used in early assessment is the Headroom Method, which uses broader estimates of potential by determining the maximum reimbursable price of the new device, and is especially tailored to the early assessment needs of medical devices. There is also a focus on studying the impact of different types of uncertainty in development on decision making, for example, by eliciting the willingness to pay of decision makers for additional information to avoid uncertainty, such as value of information (VOI).

Clinical Considerations. Clinical assessment methods in early development are, next to the classical clinical trials, those performed

in a controlled laboratory setting such as bench studies, where the performance of the medical device is compared with a gold standard, or clinical practice. Although findings of this review show that clinical effectiveness assessment of the medical devices starts late, at the prototype product development phase, in practice clinical research is also a part of methods assigned to other aims, such as CEA, or cost-benefit analysis (CBA).

DISCUSSION

The overall aim of this study was to describe the current state of the art in early assessment and to identify assessment methods that help to inform the early development of medical devices so that medical devices are less likely to be market failures and more likely to be approved by regulatory and reimbursement agencies. This study yielded 113 papers on early assessment. As can be expected, most studies were aimed at informing manufacturers of medical devices on the potential of their device. Kazanjian and Green (71) recognized that manufacturers usually have a quite restricted viewpoint during development, which mainly focuses on demonstrating proof of concept of the technology. Early assessment can partly overcome this by evaluating a device in its clinical setting, within the current healthcare market and with respect to its potential for bringing benefit to the company and society (3). Although there is also lack of any evidence on how effective the identified assessment methods are and what is their actual influence on the decision-making process, different studies stress the need for manufacturers to systematically acquire information to feed their decision-making process in early development (3;9;10;39;122;123). The question on how the effectiveness of this early evidence could possibly be measured is open for further research.

Analysis of study objectives within early assessment of medical devices showed that studies into the strategic issues within the healthcare context and studies on the economic impact of medical devices are well represented. Exploration of the potential of a medical device from a strategic perspective is often used in business plans, to identify the main barriers for successful development in all stages of development. The focus on demonstrating economic impact from a societal perspective in early assessment is probably explained by the current paradigm in traditional health technology assessment, in which demonstrating cost-effectiveness of drugs is an important hurdle to reimbursement (12;31;32;34–36).

Although individual methods might be well developed, there is no agreed-upon theoretical framework for early assessment. The interest in early assessment from a scientific perspective has resulted in the proposal of multiple, sometimes overlapping frameworks (9;13;19;63–66;70;71;77–81;83;84). The lack of uniformity to the process is also related to the dynamic nature of the device development process which requires flexibility in the assessment process (9;17;22;47–52). Medical devices are changing rapidly during their life cycle due to incremental product improvement, and they constitute moving targets for assessment (4;81). However, until a more unified theory behind the practice is developed and tested, the benefits of early assessment are difficult to evaluate. At present, there is no external motivator for manufacturers to perform early assessment and its implementation depends on demonstrating value in practice (19;39;80).

One of the biggest challenges in early assessment is the way to handle uncertainty in interpreting the results (10;14;124). High uncertainty is inherent to the early development stage. If the uncertainty is not handled well it might cause misleading results in demonstrating future clinical and economic benefits, increasing the risk of making "wrong" decisions (2;3;9;81). However, the presence of uncertainty in the input parameters for early assessment should not result in refraining from analysis. Rather than trying to make decisions in the absence of evidence, one should attempt to estimate the influence of uncertainty and quantify or qualify its influence on decisions to be made in further development.

One important limitation in this study might be a publication bias. Because of the competitive nature of the medical device development process, manufacturers shield their information from others. It is unlikely that a manufacturer would allow publication of early assessment results before the device has reached the market, or has failed. Another limitation might be the search sensitivity, for example, due to the incorrect choice of the keywords or construction of search strategies.

CONCLUSIONS

The main target audience for early assessment are the manufacturers. Most application papers aimed at reporting on the potential applications or improvement directions for a medical device(s), development of a framework for early assessment of medical device, or stakeholders perspective inclusion in further development of a medical device. In most of the cases, application papers did not specify the stage of device development or they reported that the early assessment took place in the prototype product development phase. There is great diversity in the methods used in early assessment. Qualitative and quantitative research methods were about equally applied in the different stages of medical device development, but they differed based on aims. Early assessment includes a strategic analysis (with stakeholders analysis) of the medical context, evaluation of the economic impact and early assessment of clinical effectiveness of the medical devices under development. All the methods identified aim to reduce uncertainty in the developmental stage of a medical device. To inform strategic considerations, literature review and methods focused on stakeholder involvement (e.g., focus groups, interviews) were used frequently. CEA together with the Headroom method were often used as an economic evaluation methods, while clinical effectiveness of new devices was measured through clinical trials and bench studies.

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Early assessment of medical devices under development holds the promise for more informed decisions, that could improve the pace and the efficiency of the development and guarantee successful implementation in the future. However, there is no well-developed framework for early assessment, which makes evaluation of its value difficult. For early assessment to become a practical tool to support manufacturers in medical device development, some basic classification and harmonization of methods are necessary.

SUPPLEMENTARY MATERIAL

Supplementary Tables 1 and 2: http://dx.doi.org/10.1017/S0266462314000026

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CONFLICTS OF INTEREST

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