Health Technology Assessment of Medical Devices during Development

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Chapter 1: General Introduction

1. Medical devices, market and industry

1.1 Medical devices, definitions and scope

The definition of medical device, as adopted from the one presented by the European Commission (Directive 93/42/EC) is: “any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings”. Medical devices are thus intrinsically diverse, ranging from simple devices, such as disposable syringes, to the medical aids, implants and in-vitro diagnostic tests, and finally the complex medical devices, such as imaging equipment, and robotics.

The medical devices market is one of the fastest growing and most complex in the world [1, 2]. A market that develops continuously in parallel with advancements in medical practice [1]. The global medical device market is expected to grow at a compound annual growth rate (CAGR) of 4.1% annually, and reach the total industry sales to \$477.5 billion by the end of 2020 [3]. These sales figures are being achieved by an industry that comprises more than 27,000 medical device companies worldwide and employs altogether about one million people [4]. Around 46% of global medical device sales revenue comes from sales in both Americas and 29.5% from sales in Western Europe [5]. In Asia the sales revenue is equal to 18%, in Eastern Europe it is 4.5%, and finally the sales revenue in Middle East and Africa accounts only for 2% [4].

Currently there are around 2,000 different types of surgical instruments, 450 implants using different material, and over 1 million different marks, models, and sizes of medical devices on the global market [6]. In the past the success of medical device industry was mainly focused on the development of technologies geared toward extending and improving the quality of patient's life, e.g. minimally invasive surgical devices or rehabilitation devices. Nowadays, however, this focus is shifting towards the development of technologies that fit within the integrated digitalized platforms, i.e. location agnostic technologies that will enable coordinated care [7].

Based on the definition of a medical device it is apparent that significant differences exist between the various types of technologies, their type of use, their attending risk-benefit profiles, and their required development and commercialization activities [8]. In addition, medical devices can also be classified regarding their societal impact

or the ability to completely change clinical practice (disruptive vs. incremental innovation). Finally, medical devices can be categorized based on their impact on resource use (big, medium and small ticket) and how they relate to existing technologies (new, substitute and add-on) [9]. For instance, big ticket devices refer to those which are extremely expensive for both the patient and healthcare system (e.g. CT scans). Such distinction is useful because new solutions that challenge existing paradigms and revolutionize the way treatments are administered are more difficult to manage [8, 10, 11].

1.2 Medical device industry

The global medical devices industry is relatively new and highly fragmented. It is characterised by the presence of a few large companies and a large number of small and medium sized enterprises, i.e. SMEs (80% of companies <50 employees), which are responsible for the development of the technological breakthroughs of today's healthcare market [1, 6, 8, 13]. Those SMEs, however, have limited resources to demonstrate the evidence on safety and efficacy of medical device to meet the regulatory requirements, and in the face of a failure on the marketplace it is difficult for them to survive [1, 13]. The research and development (R&D) spending in the medical device industry, as a percentage of sales, is nearly 12%, however, most SMEs research focuses on factors that contribute to their survival such as financing, rather than a greater understanding of the medical device innovation development process [8, 14].

2. Challenges for medical device development and market access

The medical device industry faces many challenges as the industry is under intense scrutiny and regulation. Manufacturers have to meet the regulatory issues regarding safety of medical devices, while in the same time they have to demonstrate the devices cost-effectiveness and potential benefits to the healthcare payers and purchasers.

2.1 Regulatory challenges and safety of medical devices

The medical device industry is one of the most strictly regulated industries [8]. The responsibility for the medical devices regulatory cycle is usually assigned to three organizations: competent authorities, manufacturers, and third party certification

organizations, i.e. notified bodies [15]. The regulatory framework reflects the healthcare system of particular country and influences manufacturing, the quality system, labelling, the clinical data required, fees (during the approval process), the modification pathway, i.e. how the following generation will be designed, among others [15]. In the USA, for example, Food and Drug Administration (FDA) makes sure that medical devices are both effective and 'reasonably' safe, i.e. the benefits they bring outweigh the risks of the device use. In the same time in Europe manufacturers must only demonstrate that the device is safe and performs according to its intended use, i.e. it does what is supposed to do when it is used as directed [15]. The EU legislation states that the introduction and assessment of medical devices depend on a "suitable, robust, transparent and sustainable regulatory framework for the benefit of European patients, consumers and health care professionals, adapted to the needs of tomorrow [16]. Those different approaches result in significant differences in the amount of tests devices must pass, and the speed of introduction of the devices into the market. In fact in Europe medical devices are on average introduced two years earlier than in the USA [15]. In the same time different medical device classification can significantly impact the approval path, e.g. a device in the US could be considered a drug in the EU.

Recently the effectiveness of the existing regulatory frameworks have been the topic of various debates in the USA and in EU, with the focus on the jurisdictions to ensure the performance, safety, and quality of new devices [17]. In the USA, for example, the Institute of Medicine (IOM) proposed to eliminate FDA's 510(k) clearance process as an unreliable screen for the safety and effectiveness of devices [17, 18]. In the same time the industry biggest concern relates to the fact that the USA regulatory system is too slow, risk adverse, and expensive [17]. Compared to the USA, the EU regulatory processes are somewhat faster for medical devices. That way some high-risk technologies can be placed earlier on the EU market (e.g. coronary stents, replacement joints) [17, 19]. In the same time, an EU regulatory framework for medical devices, which is based on the Conformité Européenne (CE) marketing process, is also criticised as an inadequate to provide sufficient safeguards for technologies that affect morbidity, mortality, and health-related quality of life [17, 19, 20]. The inadequacies are resulting from inferior regulatory evidence standards, non-transparent decision-making processes, and insufficient post-market surveillance [17, 20]. To address those concerns the European Commission proposed to "adapt the European regulatory framework in order to secure patients' safety while favouring innovation" [21]. However, recently various medical devices were recalled from the market in Europe, e.g. articular surface replacement hip, prostheses, and Poly Implant Prothese (PIP) breast implants. As many of those devices were denied

approval by the FDA, that have further heightened concerns about current regulatory practices in EU [17, 19, 22, 23]. However, as the regulatory pathways are becoming stricter, a dilemma between the safety considerations and the delayed benefits for the targeted patients or users through delayed introduction of potentially beneficial medical devices arise [16].

Box 1. Regulatory hurdles: Breast implants example [22].

In the years 2011-2012 tens of thousands of defective breast implants were recalled in Europe. In the same time a new data on risks have raised questions about regulatory standards for the medical implants in the USA and European Union (EU). In the USA breast implants are regulated as high-risk medical devices that must be proven reasonably safe and effective in clinical trials and subject to government inspection before they can be sold. In contrast, clinical trials and inspections have not been required for breast implants or other implanted devices in the EU; approval is based on other information. As a result of these differing standards, the breast implants that were recalled across Europe had been removed from the market years earlier in the USA than in the EU, a decision USA government health agencies can point to with pride. However, neither the EU nor the USA has used their regulatory authority to ensure the long-term safety of breast implants. Only in 2012 the EU announced regulatory changes that could improve that situation.

2.2 Challenges with reimbursement and evidence development

Medical device innovations have a great potential to bring future benefits to patients. However, having a unique product or technology is not enough to guarantee success within the healthcare sector. The manufacturers must prove that their innovative medical device has a significantly high perception of value to all stakeholders in the healthcare to secure its successful implementation, reimbursement and acceptance by future users [1]. There are several issues that present challenges to manufacturers and HTA bodies, i.e. (1) fast changing technologies prevents evidence development strategies used in pharma, (2) many medical devices offer convenience benefits rather than improved health outcomes, and (3) medical devices are increasingly considered as a part of care-pathway which requires evaluation of services rather than the device as an isolated technology.

Medical devices are often fast changing technologies, and their lifespan varies from few seconds for disposable devices to several decades for some of the implants and hospital equipment. From idea generation to obsolescence, many medical devices have relatively short product cycles of 2.5 years on average (ranging to up to 6 or 7

years for imaging devices) [6, 8, 24-26]. It means that the device manufacturers have little time to recover the investments. In the same time the development of medical devices is characterised with the constant flow of incremental product improvements, which can make comparisons of those devices with adequate controls difficult or unethical [24, 25]. For the manufacturers it is thus challenging to conduct randomised controlled trials (RCTs) of modified devices to prove the value of their improved products [2]. On the other hand, for the devices undergoing incremental changes the “learning curve” in their use will not impact the organisation of healthcare delivery centres in which previous generation technology was already implemented and that could ease implantations significantly [2].

Many medical devices offer improvements over current care in terms of “convenience” for the patients and “improved process of care”. It may thus be very difficult to assess the value of those devices using standard methods of economic benefit measurement, e.g. the quality-adjusted life-years (QALYs). It can also apply to the diagnostic medical devices, as the value they provide to the patients with an improved diagnosis is very difficult to separate from the value of the improvement in patient outcomes, resulting from subsequent treatment [2]. It is thus feasible to measure and value the attributes of devices using alternative approaches to standard quality-of-life measures, such as willingness-to-pay studies or discrete choice experiments [27]. However, this approach is not yet fully explored. In the same time the medical device industry observes a shift in the value based reimbursement paradigms, where the value-based pricing approach to medical device development and implementation is slowly replacing the dominating cost-plus pricing approach [28].

Finally, medical devices are increasingly seen as an element of a care pathway, which requires the evaluation of the process of care rather than the single device. In that sense, an implementation of a new therapy or service involving a device can have wider economic implications for the organisation (e.g. workflow improvement in the hospitals) and financing of healthcare (i.e. new reimbursement schemes needed) [2]. In the same time, the financing of those devices where the service, not the technology itself represents the health care benefit must be investigated in both the terms of procurement and reimbursement. Procurement is focused on establishing the device price between the producers and providers of health care services (e.g. price setting and negotiation) [29]. Reimbursement, on the other hand, is comprised of coverage, which is the essential first step that drives subsequent coding and payment procedures, i.e. the medical device that is not covered by insurance plans, will never be reimbursed [30].

3. Early Health Technology Assessment of Medical Devices

3.1 Health Technology Assessment of Medical Devices

Health technology assessment (HTA) is a form of policy research that studies short- and long-term effects of healthcare technologies in a systematic and multidisciplinary way. It serves as a decision aid tool to assist in the adoption, allocation, and funding of both new and old health technologies [31]. Traditional HTA, well developed in the pharmaceutical industry, involves the assessment of new health products when they first come into the market, and as such it mainly supports decisions on the coverage and adoption [32-34]. It consists of evidence production (concerning the development, consequences and conditions for implementing technology), the evaluation of this evidence from a societal perspective leading to further clarification or refinement of the issues involved in balanced decision-making, and finally the recommendations made to politics and society [24, 31, 35, 36]. The evidence gathered during the HTA process can come from various sources, such as randomized clinical trials, comparative studies, case studies, independent expert opinion, and reports from expert committees. HTA can be technology oriented (e.g. magnetic resonance imaging), health problem-oriented (e.g. diagnostic procedures for breast cancer), or project-oriented (e.g. planning for procurement of equipment) [37].

Based on the specifics of medical devices, there are a number of methodological considerations that require a tailored HTA, differing from the approach taken for pharmaceutical products. For example medical devices are often diagnostic devices or they only have an indirect impact on patients outcomes through ease of use or better systems performance (e.g. ventilator in OR). In those cases the measure of health outcomes for medical devices is very challenging. Furthermore, experimental studies (e.g. RCTs) are more difficult for medical devices as their performance highly depends on end-users, and thus the learning curve have to be considered [2, 38, 39]. These differences have an impact on the selection of the timing of the assessment, the methodology, the study design, and the patient population [24].

3.2 The case for early Health Technology Assessment of medical devices

HTA could be a valuable tool to inform decision-making process throughout the development process of medical devices, starting at the early lifecycle stages. Applied iteratively, HTA could help manufacturers to gather new and valuable

evidence from diverged external and internal sources. That way they could make better informed decisions regarding, e.g. the medical device development (device design and usability), the choice of potential implementation area, or the choice of the appropriate reimbursement schemes. In addition, the earlier an assessment starts, the more likely device development diffusion can be curtailed if it is unsafe or ineffective and a significant amount of investments can be saved or channelled towards more promising technology development [25, 32, 36, 40, 41]. Early assessment could also provide answers for political decision makers and insurers on the issue of funding new devices and could allow early access of patients to most beneficial technologies [24]. However, the field of an early assessment of medical devices, referred also as early HTA, is relatively new and unexplored. It thus makes an establishment of an interactive HTA process that would fit various stages of the medical device development, and would be clear to follow by the SMEs, a very challenging task.

3.3 New product development (NPD) in medical device sector

The medical device development process is inherently complex and it is evolving quickly, with new findings in the area of biotechnological research being published every day [8, 42]. That makes it very dynamic, and requires constant integration of new evidence. Iterative nature is a distinguishing characteristic of the medical device development process [8]. Iterative approach builds on the idea that at the company level decisions as to whether and how to proceed with the development may be reviewed on the basis of new evidence that becomes available in the lifecycle of a technology [40]. In many cases, medical devices are actually developed in several generations, through the continuous (incremental) innovation process [6, 8].

For reasons of simplicity, the development of medical devices can be presented in a form of a linear development processes with distinguished stages separated by the decision gates (figure 1) [32, 43, 44]. However, the linearity of the medical device development process, as depicted in figure 1, rarely occurs in the real life [45]. The development process begins with an “idea generation” and ends with “post-marketing surveillance” [43, 44]. The gates serve as a decision points, at which the development can be continued or abandoned. At each decision point, new evidence that has become available since the previous decision point can be taken into account and in this way management flexibility can be included [43]. The number of stages in the lifecycle of medical device is an on-going debate [46, 47]. The knowledge of the medical device lifecycle, i.e. the consecutive and interlinked stages

of development, from raw material acquisition to final disposal, is important to help manufacturers to develop devices that are safe, effective, and efficient to use [15].

Recently, the early development stages, were recognized as the most critical ones in the development process, as they mainly focus of on knowledge acquirement that serves to evaluate the idea behind the device development [44]. During those early stages “potentially lucrative ideas” are identified and prioritised. For that reason in the early stages the whole innovation process can either be initiated or broken down.

Figure 1. A simplified flow-chart of stages in medical device development (adapted from IJzerman and Steuten [32]).

4. Toward an early lifecycle assessment of medical devices

In developing and executing the development strategy for medical devices, manufacturers should identify early-on the outcomes (i.e. endpoints) that will most likely be used by regulators and payers to evaluate the device and try to understand what underpins these outcomes [8]. A clear and systematic understanding of the relationships between the engineering, clinical, and economic aspects of the device, and the impact of early stage decisions (e.g. future users) on the identified outcomes of interest is crucial [8]. Several studies were conducted in recent years to answer the question of which methods, and at what time, can be used most appropriately to support decisions regarding the development of medical devices [32, 48, 49]. In

those stepwise approaches, evidence gathered at each stage fed the information into the next stages in order to reduce uncertainty and aid decision making throughout.

However, as the iterative use of Health Technology Assessment is relatively new and unknown, many questions remain. This thesis particularly addresses the (1) clinical need and methods to engage various stakeholders within the medical device development and (2) the development of the commercial viability of medical devices at the early stages of the development to prioritize development of the most “beneficial” technologies using potential added value to society and, hence, economic returns.

4.1 Engaging stakeholders to define clinical need

An early assessment ideally should start with a clear picture of the clinical need that medical device could fulfil. This obviously goes beyond the demand of a single stakeholder group. The clinical need should be supported with the evidence on medical device added value (e.g. clear health benefits for patients), its quality compared to the competitors, its uniqueness and innovativeness. Clear definition of the clinical need should help manufacturers to define the implementation area for the device, and its future application, and based on that they could start gathering an essential knowledge on the fit between the medical device and the healthcare market. It is essential that manufacturers take into consideration the future users of their technology (e.g. patients, specialists) and the associated learning curve (i.e. the rate of a person's progress in gaining experience or new skills), the fit between the device and its future environment (e.g. work procedures), and the fit with the healthcare regulations. All those issues can be covered with a thorough stakeholder's analysis that should be applied iteratively throughout the device development process.

4.2 Iterative health economic modelling; the use of portfolio prioritization methods

The economic evaluations of the medical device early on in the lifecycle is an important factor in the development of its commercial viability, i.e. the ability of a device to compete effectively on the market and generate sustainable revenues. To perform an economic evaluation of medical devices manufacturers must build a thorough understanding of the market and potential competitors of their technology. Based on that they should gather information on the competitors prices, and the

willingness of potential buyers to pay for the device. That way they can establish the price margin for their new technology early in the development. The margin price together with revenue market size, on the other hand, can give them a good indication of potential return on investment they could expect once the device would be implemented. In the same time, however, manufacturers must also analyse if their device after implementation will not create potential burden for patients, and if it will fit within the existing reimbursement schemes.

5. Objectives and outline of this thesis

In this thesis, the fundamental idea of an early assessment process of new medical devices is investigated in detail. The overall objective of this research was to explore the concept of early HTA of medical devices, and to study several elements of which an early assessment may consist of. The aim of chapter 2 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 fail at market launch and more likely be approved by reimbursement agencies. Chapter 3 synthesizes the results of a survey on assessment practices of medical devices in the early phases of the development process within the biomedical companies in the Netherlands. The outcome of that study provided useful contribution to understanding of current early assessment practices, how its results influence the development of medical devices and lead to areas of improvement. In chapter 4, we investigated whether and how an iterative approach for capturing stakeholder's perspectives during the design and development of medical device can be helpful to identify potential clinical need for new medical device. A 3-step approach to involve stakeholders in medical device development was introduced and tested during two distinct early stages of medical device development. Chapter 5 introduces the headroom calculation combined with the Return on Investment analysis (ROI) as a simple, yet straightforward approach to analyse the potential commercial viability of two disruptive and four incremental medical devices in different stages of early development and to study the impact of the results of such analysis on actual R&D decision making within the manufacturers companies. Finally, chapter 6 introduces a scoring model that can serve as a potential guideline to determine likely success on the market of a medical device in the development. The model is based on an existing NewProd model, which is widely used within various industries. However, to fit the specifics of the medical device industry the factors used within the model were adapted, and the model was re-designed to be applicable at different stages of the medical device development. In

addition, the model analyses the evaluation efforts of the project teams and gives recommendations on potential assessment activities which could be conducted for more thorough evaluation of medical devices. The adaptation of the model was based on the research conducted during the whole path of the PhD. To adapt the structure of the model the interviews within the medical device industry were partially used together with the systematic literature review (Chapter 2 and 3). The list of an assessment activities was extracted from the literature review (chapter 2), evaluated during the interviews within the medical device industry (chapter 3), and several methods were tested on a real case study examples (chapter 4 and 5). In Chapter 7 the findings of this thesis are discussed and recommendations for implementing early assessment activities in practice and recommendations for further research are given. Finally, the thesis summary can be found in Chapter 8.

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Chapter 2: Medical Devices Early Assessment Methods: Systematic Literature Review.

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ABSTRACT

Objectives: 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 computerised 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 1961 articles identified, 83 studies passed the inclusion criteria, and 30 were included by searching reference lists. There were 31 theoretical papers, and 82 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.

1. INTRODUCTION

Each year huge number of medical devices are being developed, but only 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 the development seems 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 judgement 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].

Figure 1. A simplified flow-chart of stages in medical product development based on IJzerman and Steuten, 2008 [10].

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 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.

2. METHODS

2.1 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 early of development.

A systematic search strategy was conducted in September 2013 using (1) computerised databases (PubMed, Science Direct, and Scopus) and (2) reference search of included articles. Search strategies were build 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. Further, reference lists of included papers were hand searched.

2.2 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: (1) the articles written within the healthcare context; and (2) 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.IJ.). 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.

2.3 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.

2.4 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 Pate-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 pre-specified but categorised on the basis of the data obtained.

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

3. RESULTS

3.1 Literature search strategy

Figure 2 presents a flow chart of the literature selection procedure. The systematic literature search yielded 1961 hits. 83 articles immediately met the inclusion criteria and were selected from the search strategy. Another 30 articles were selected based on screening of the references in the selected articles. 82 out of the 114 selected studies were application papers, and 31 studies were theoretical papers.

Figure 2. Flow chart: selection of the literature.

3.2 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. 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 [30 articles]. Although it was decided that these paper 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 [20 articles]. Some frameworks propose to support decision-making process 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 [18 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].

3.3 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. 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.

3.4 Main objectives of early assessment

3.4.1 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 analyse 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 modelling/statistics, which is based on modelling 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.

3.4.2 Economic evaluations

Economic evaluation is in its nature a quantitative method. 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, e.g. by eliciting the willingness to pay of decision-makers for additional information to avoid uncertainty, such as VOI.

3.4.3 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 to 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).

Table 1: Study objectives in selected articles according to addressed main target audience.

Main target audience/Study objective	Decision makers on coverage and reimbursement		Policy makers		Manufacturers		Varied	
	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;	

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) [III]; 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 (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];

4. 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 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 manufacture would allow publication of early assessment results before the device has reached the market, or has failed. Another limitation might be the search sensitivity, e.g. due to the incorrect choice of the keywords or construction of search strategies.

5. 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.

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 is necessary.

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Chapter 3: Early Assessment of Medical Devices in Development for Company Decision Making: An Exploration of Best Practices

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ABSTRACT

Background: In order to secure successful development and implementation it is suggested that medical device manufacturers should start gathering evidence on devices effectiveness and efficiency at the early stages of development. This aim of this study was to analyse whether and how manufacturers in the Netherlands perform an early assessment of medical devices.

Methods: Semi-structured interviews were performed with the key-informants from medical device companies with experiences on different aspects of the medical device development and implementation. The primary focus of an interviews was to identify reasons why, how and to what degree these informants were engaged in early assessment of their medical devices. Furthermore, the type of early assessment activities within companies regarding the clinical context, the market and its stakeholders, and the health economic impact were analysed.

Results: 37 interviews were performed with key-informants of the 36 medical device development companies in the Netherlands, out of which 19 small and medium sized companies (SMEs), six large companies, and 11 spin-offs. The majority (N=19) of the companies are using both the internal resources and external consultants to perform early assessment activities. An analysis of the clinical context, potential market (N= 25) and stakeholders analysis (N=18) most often starts at the idea generation stage of medical device development. The analysis of the health economic impact of device under development usually starts at the idea generation stage (N=15) or before the prototype development starts (N=14). Most companies extend their assessment activities until the post-marketing surveillance phase (N=30-31). The least developed areas of the assessment are economic evaluation from the societal perspective, and the stakeholders analysis.

Conclusions: Although many methods seem to be in use within the medical device industry, there is no clear understanding of how those methods are understood and conducted, what evidence manufacturers are actually gathering with their use, and how they influence the decision-making process within the companies. A simple guidelines helping manufacturers to understand which steps should be taken from the early development stages might greatly benefit the whole industry.

1. INTRODUCTION

Medical devices play a crucial role in the continuing advancement of healthcare, providing new solutions that challenge existing paradigms and revolutionize the way treatments are administered [1-3]. The medical devices industry is now seen as one of the fastest growing ones, with the technological advances driven by an increasingly demanding market with growing patient population and legislative requirements, amplifying health policy reforms, and tough quality and regulatory hurdles [4-8]. A multitude of medical devices appears on the market every year, where medical devices are defined by the European Commission as “any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings” [9].

To enter the market, a device manufacturer must demonstrate that it is safe, that it produces value to patients and society at a reasonable cost, that it has potential to bring significant savings to the healthcare system, and that the risks associated with its use are acceptable when weighed against the benefits to patients [7]. Health Technology Assessment (HTA) is the scientific discipline to systematically collect evidence on the effects, risks and health economic consequences of new medical technologies [10]. Over the past decades, it has been difficult for small and medium sized companies (SMEs) that constitute around 75 percent of the medical device industry, to implement HTA in their business process [5]. Those SMEs operate under constant financial pressure [1,5,11].

However, although HTA is not a core activity in most SMEs it is expected to become more important in the near future. A recent Dutch report reflects on the need for generating clinical evidence on safety and efficacy before market launch of medical devices, as do other policy documents such as the recently revised regulations in the EU urging for collection of clinical evidence throughout the market lifetime of a device [12,13]. All these developments witness the current debate on safety of medical devices and the problems identified in the current regulatory framework.

So far, knowledge on HTA in SMEs is limited. In 2012, Craven et al. [14] explored the levels of health economics knowledge within English SMEs. The results revealed that 60 percent of SMEs representatives had low or no HTA experience. Clinical trials and cost analyses or cost-effectiveness studies were the most highly cited means by which SMEs aim to demonstrate value of medical devices to the

purchasers. However, those methods were reported as having no formal influence on the decision-making process within SMEs.

Ideally, HTA should be conducted as early as possible in the device development process [15-17]. That way the development can either emerge or be stopped without major financial drawbacks for the company. The requirements of the stakeholders should constitute a base for an assessment and can be used to prioritize the development of medical devices most likely to succeed among others. At the same time, medical device manufacturers could use the early evidence gathered to enhance the efficiency of the use of research and development (R&D) resources within the company [15,16,18].

This aim of this study was to analyse whether and how medical devices manufacturers in the Netherlands perform an early assessment of medical devices that would allow them to meet the requirements of potential stakeholders. The Dutch medical device industry market was chosen, because of the large amount of public-private partnerships present in that market, e.g. The Centre for Translational Molecular Medicine (CTMM).

2. METHODS

2.1 Exploration of early HTA assessment methodologies in selected companies

Four areas of an early assessment of the medical devices were subject of this study and incorporated in the structured interviews: (1) analysis of the clinical context of medical device use; (2) market analysis; (3) stakeholders analysis; and (4) financial and health economic evaluation of new medical device. In addition, the interviews were held so that a better understanding of the specific role of early assessments in companies could be elaborated. A detailed map of the four topics for early assessment as well as the specific elements is provided in figure 1.

Figure 1. The areas of an early assessment of medical devices as distinguished in this research.

The analysis of the clinical context of medical device included the criteria used by the companies to evaluate clinical impact and the clinical need for the novel medical device, e.g. the underlying disease state and disease severity. The market analysis as a part of an early assessment in this research was assumed to be based on the analysis of main competitors and the analysis of the future users. The stakeholders' analysis was assumed to be based on the opinions of the experts, and the opinions of the decision makers. Finally, in the financial and health economic methods the company financial prospects as well as the buyer and societal perspective were analysed. The list of methods presented during the interviews was extracted from the literature, and it was complemented during the validation of the interviews, and during the interviews themselves, as participants were asked to add methods if they thought any were missing. In general, specific methodologies (e.g. the Headroom method) were not explicitly included, as some of them might not be familiar to the medical device companies employees, so short description of the practical aims and results of those methods were used instead. During the interviews participants were asked to select those methods from the list which are being used in the company to assess medical device. Finally, the participants were asked to indicate at which stage the company started and finished specific assessments as well as which assessments were carried out iteratively throughout the development cycle. Six roughly defined medical device development stages were: (1) idea generation; (2) before prototype development starts; (3) during the prototyping; (4) gathering evidence on device effectiveness and efficiency; (5) device marketing; and (6) post-marketing surveillance.

2.2 Interview design and selection of participants

This research was based on semi-structured face-to-face interviews with key-informants within medical device companies in the Netherlands. “Key-informants” in this study were defined as those people within the medical device companies who have experience-based and/or professional-based knowledge on different aspects of the medical device development and/or implementation, e.g. assessment practices, regulatory access, reimbursement [19].

After designing the interview format, all questions were pilot tested by experienced representatives in academic science and in the medical device industry, based in the Netherlands (3 people), and in the United Kingdom (1 person). The objective of the validation was to make sure that the questions covered the full range of methods and that the content of the questions will be easily understandable to the key-informants, i.e. in case of no scientific background in the early assessment of medical devices topic.

The participants of this study were selected with the use of the convenience sample method, based on the structured search of biomedical companies online. In total 91 companies were selected. The Chief Executive Officers (CEOs), or Managers within the topic of interest, of those companies were identified with the use of LinkedIn service and contacted via the telephone, with the use of the number provided on the companies websites. During the phone conversation the CEOs were first introduced to the research topic and asked about the willingness of their company to participate in the study. After the approval of the CEOs, the researchers scheduled the face to face structured interview with the CEOs themselves, or contacted the person indicated by the CEOs as the key-informant. In total 36 CEOs were interested in the participation, with one large company indicating two people from two different departments as key-informants for the interviews. 37 face-to-face structured interviews were conducted. Before the interviews, the interviewer explained the purpose and format of the interview to the participants. The interviews lasted on average around 50 minutes. The interviews were audio recorded with participants’ permission. The results of the interviews were analysed with the use of the SPSS Statistics 21.0 software.

3. RESULTS

3.1 Company and participant's characteristics

The interviews revealed that the majority of the companies commission their own employees as well as external consultants for the early assessment (reported 19 times). 15 participants reported that an early assessment is being performed only by people employed by the company, while only three stated that early assessment activities are fully performed by an external consultant. Interviews revealed that the main reason for the companies to search for an external help for the early assessment of medical devices is the lack of an expertise within the company (N=18). Some participants stated that hiring external assessors is more efficient, e.g. cheaper (six participants), or more time-efficient (mentioned twice). Internal assessments are mostly performed by an individual employees assigned to particular tasks (N=22), or performed within the specialized departments within the company, e.g. R&D and Sales and Marketing department (N=14). Six participants stated that an early assessment in their companies is performed by assigning particular tasks to multiple people. Finally, two participants admitted that they are not sure how an early assessment was organised within their company.

3.2 An early assessment methods used within the companies

3.2.1 An overall assessment activities conduction

When asked to indicate the start of the assessment activities based on six roughly defined medical device development stages, it seemed that clinical context and market assessment have the highest priority, as both start at idea generation for the majority of companies. A smaller number of companies also start stakeholder analysis (n=18) and financial and health economic evaluation at the idea generation, while more companies postpone this to later stages. Figure 2a presents an overview of the stages where an assessment within four areas of an early assessment started as reported within the Dutch medical devices industry.

Figure 2a. An overview of the starting time of an assessment activities within four areas of an early assessment as indicated by the interviews participants.

When asked to indicate when the assessment activities stop, the majority of the participants (reported 30-31 times) indicated all the areas of an assessment activities last until the post-marketing surveillance. Figure 2b presents an overview of the ending time of an assessment activities within four areas of an early assessment as indicated by the interviews participants.

Figure 2b. An overview of the ending time of an assessment activities within four areas of an early assessment as indicated by the interviews participants.

3.2.2 Clinical context assessment

To analyze the clinical impact and need several performance indicators were of interest to the medical device manufacturers: (1) potential device efficacy/effectiveness (N=32), (2) potential target population size (N=30), (3) safety and tolerability of the device (N=24), (4) patient satisfaction with the device (N=23), and (5) the severity of the disease that medical device is targeted at (N=15).

In order to evaluate these indicators, companies use different information sources, e.g. talking with the patients and clinicians (key-opinion leaders, KOL) (N=22), attending (clinical) conferences, events/trade shows (N=21), and reading scientific journals (N=20) (see figure 3).

Figure 3. An overview of the information sources used to assess the clinical impact criteria within the medical devices industry.

3.2.3 Market assessment

The market analysis as a part of an early assessment in this research was assumed to be based on the analysis of the future users and the comparison to other interventions used for the disease. The majority of the respondents reported that the user analysis is mainly based on literature reviews of user needs (N=32), safety and usability testing (N=31), and informal and/or accidental meetings with users (N=29) (see figure 4a). The analysis of the alternative medical devices and interventions is mainly based on experts (KOL) consultation (N=30), monitoring industrial news sources (N=27), and patent searches (n=26) (see Figure 4b).

Figure 4a. An overview of the methods used to assess the future users' perspective of medical devices under development.

Figure 4b. An overview of the methods used to assess potential competitors of medical devices under development.

3.2.4 Stakeholders analysis

The analysis of the stakeholders within the medical device industry is based on the views of the experts and key decision makers within the medical device field of application. The participants reported that two dominating methods were present to gather those opinions, i.e. informal discussions (N=22), and formal consultation (n=21) (figure 5).

Figure 5. An overview of the methods used to gather the opinions of experts and decision-makers.

3.2.5 Financial and health economic evaluation

With respect to the financial analysis, most participants reported that in their company an extensive financial analysis from the company perspective is conducted (N=34), followed by financial analysis from the buyer (health insurance or hospital) perspective (N=29). Finally, least interviewees reported a full health economic evaluation, i.e. an evaluation of the incremental societal benefits against the incremental costs to society (N=22).

The financial analysis from the company perspective is usually supported by three methods, i.e. price determination (N=31), net present value using discounted cash flow analysis (N=30), and return on investment analysis (N=29) (figure 6). The financial analysis from the buyer perspective is supported with the Budget Impact Analysis (N=29), and with the return on investment (N=21). Interviewees reporting on a health economic evaluation did mention cost-benefit analysis (N=18), cost-effectiveness analysis (N=16), and use the least – cost-utility analysis (N=7).

Figure 6. An overview of the methods used to perform an economic evaluation from the company perspective.

4. DISCUSSION

With the increasing regulatory demands for medical device SMEs and the need for efficient allocation of resources, a thorough understanding of the regulatory environment and its mechanisms to build the evidence at early stages of product development is required. This study interviewed key-personnel from medical device companies involved in R&D and market access and concluded that most companies do several assessments along the product development pipeline. Most of the assessment activities start early in the development of the medical devices (at the idea generation stage) and are conducted iteratively up to the post-marketing surveillance stage.

Although this research was not solely focused on SMEs, more than half of the companies participating in this study were SMEs (N=19), and 11 were a micro-sized spin-off companies with less than 10 employees. Almost half of the interviews participants, which were selected as the “key-informants” in the topic, reported a medium level knowledge (N=18) of the medical devices health technology assessment procedures, and one fourth indicated low/basic knowledge. This led to the conclusion that, although early assessments was considered important, most companies do not have in-house capacity and knowledge to perform health technology assessment. Previous research on the health economics activities within the English medical device industry performed by Craven et al. [14] seems to confirm the findings of this research with regard to the varying levels of health economics knowledge within the medical device industry. The main recommendation of Craven et al. was actually to increase the focus on the education needs, and tools to support the application of various health economics/assessment tools within the industry.

With regard to the different areas of the assessment activities as distinguished in this study, it is clear that the current focus is on the evaluation of the clinical context of the medical device and the assessment of the potential market. These assessments are mostly performed informally with interviews and stakeholder meetings. The majority of the companies use only the conversations with the clinicians and patients (N=22) and attending clinical conferences and trade shows (N=21) as an actual source to inform the clinical context. No formal quantitative methods presenting the opportunities for new products and the needs of patients are performed, while these could contribute to the validity and quality of the information that is collected.

The financial and business case evaluations within the medical device industry seems to be well developed with return on investment as a main driver and price

setting as the objective. Although such analysis is essential for business planning and attractive venture capital, it does not reflect the perspective of the society in which the medical devices will operate. The societal perspective, i.e. the question whether society is willing to allocate scarce resources to implement and/or reimburse the new medical device, is at best only marginally performed or understood from the companies perspective. This is disappointing, as the business case might be unreliable if the societal benefits are not considered. Markiewicz et al. proposed a simple method to illustrate how the expected societal benefits of the new product can be used for value-based pricing [23].

The results of this study confirm that medical device industry is very specific. It is characterized with very high level of innovativeness, strong technology push and a not very well developed market access and pricing strategy. It is build up mostly from SMEs managed by executives with strong scientific or technical background and over-simplified view of business and management issues [24]. That leads to the situation where other than technological advantages aspects, which significantly influence future implementation and adoption of medical device, e.g. the potential stakeholders requirements, are mostly overlooked [25]. At the same time the majority of the SMEs within the medical device industry focus on the development of a disruptive technologies, for which it is difficult to find the way to economically viable products [5]. A truly innovative medical device may offer the ability to significantly improve patients care, however proving safety, efficacy and regulatory compliance is often too challenging and costly for SMEs [26,27].

Inability of the SMEs to provide strong evidence of the potential societal value of their medical device under development makes it very difficult, or even impossible for most of them, to find investors willing to support their projects. As the healthcare resources are getting more and more stringent, the ability of a company to prove to potential investors that their technology will be cost-effective became a compelling argument supporting its future development [28]. The development of medical device from concept to product on the market can take up to a decades and significant investment is often needed before the medical device can even reach the first stage of clinical investigation [5]. In the same time the coverage and reimbursement by health insurance have a strong direct impact on the manufacturers attainable revenues [29]. Although there is a debate going on how assessment of an innovation early in the lifecycle could provide answers for insurers on the issue of funding the new technology and allow early patient access, the direct collaboration between medical device industry and insurance companies is still in the learning phase [7,30].

Although medical device manufacturers are operating in high technology multi-stakeholder environments they often fail to recognize the importance of the stakeholders analysis and they face the challenge of finding the right people to collaborate with [5]. For the medical device manufacturers it is therefore important to start an early dialogues with various stakeholders to understand the evidentiary requirements of various decision-makers involved in the implementation process. That could also help to better align perspectives on the potential value that the medical device could introduce to the healthcare system [31].

5. CONCLUSION

Although many methods seem to be in use within the medical device industry, there is no clear understanding of how those methods are conducted, what evidential requirements are to be met and how this supports the decision-making process in companies. To improve the assessment of the medical devices, a structured guidance of best practices would greatly benefit the industry as a whole.

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Chapter 4: Stakeholder Engagement in the Development of a Diagnostic Test for Kidney Disease

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ABSTRACT

Objectives: Iterative stakeholder involvement is proposed as a decision-support method to define and identify the clinical need for a novel point-of-care test to monitor patients with kidney disease (KD).

Methods: A three-step approach stakeholder involvement was used in two distinct stages of the test development: in the Targeting Product and early proof of concept stages. In the first step, the expectations of the manufacturers regarding the medical device potential were identified. In the second step, literature analysis and key-informants perceptions on relevance of the KD test were determined through structured interviews and questionnaires. In the final step, the results of the analysis were discussed with the manufacturers team and the detailed implementation scenarios were adapted based on the stakeholder input.

Results: Although patients willingness to accept the device as a daily monitoring tool for kidney function was high, the actual use would depend on clinical guidelines and physician recommendations. Family doctors did not perceive the device as clinically relevant for monitoring KD. However, manufacturers decided to continue further device development targeted for home monitoring of kidney function. Additional analysis indicated more concerns with patients ability to follow-up on results of daily screening, reimbursement of daily screening test and the shifted responsibility for care as a result of patient involvement.

Conclusions: The stakeholders seemed to have a limited ability to change manufacturers perception of most viable target application for their product. Other forces, i.e. existing and/or potential funding, and potential market size appear to be more important decision-making drivers for manufacturers.

1. INTRODUCTION

Medical device development is a staged process that begins with idea generation and ideally stops with a device being implemented on the market as a commercially viable product [1]. It is widely recognized that the involvement of stakeholders in the design and development of medical devices is important. In practice, however, the early stages of the device development are often technology driven [2]. This may be explained by the large number of product ideas stemming from university based research. Although useful and valuable, technology driven design can result in either expensive design modifications in later development stages or even a failure to reach the market [3].

One way to increase the potential commercial viability of a medical device is through a rigorous and iterative process of stakeholder involvement starting early in development [4-7]. With stakeholders known for their experience in selected clinical target areas, it is possible to identify potential future users needs, and to determine to what extent these needs and technology specifications should be taken into account in device design [8, 9]. The challenge of involving stakeholders in medical device design is thus to align the needs of the stakeholders with the potential use of the device and to ensure that device development will be commercially viable from a manufacturing perspective [8].

Stakeholders are defined as "any group or individual who can affect or is affected by the medical device irrespective of the stage of development" [6, 10]. Ideally, stakeholders should be involved in all stages of the device development, and the output should continuously be used to help manufacturers to make decisions on whether and how to proceed with the development [1, 6, 11]. However, published literature on stakeholder involvement is mainly focused on the later stages of the medical device development cycle [4, 6, 12, 13].

From the literature it can be concluded that there are a number of advantages of involving stakeholders in the iterative process of development, such as (1) a substantial shortening of the device development time by improving the efficiency of the research and development (R&D) process, e.g. through improvement in device design, usability and quality [14-17]; (2) improved access to the requirements and expectations of potential users that could result in improved device design [18]; (3) an increase in the critical thinking of manufacturers about potential implementation areas for their device at the early stages of its lifecycle [6, 8, 13, 18, 19]; (4) identification of potential problems early in the development, which, unaddressed,

could result in costly device modifications and reduction in device recalls [14, 15, 18]; (5) the generation of ideas for new products and product innovations [18]; and (6) receiving assistance to obtain funding for further development of the device by providing “experiential” evidence in the assessment process [7, 14, 20, 21]. Some of these advantages might actually benefit society as a whole [14-17].

Stakeholder involvement usually consist of a combination of both qualitative and quantitative methods, to provide the best understanding of the research problem and enhance research validity and reliability [4]. Frequently used methods in stakeholder involvement are focus groups, ethnography, contextual enquiry, task analysis, cognitive walkthrough, questionnaires, interviews and usability methods, literature search, qualitative weighting of relevant criteria, plenary discussions, workshops and Delphi techniques [4]. The decision on which methods to use depends on different factors, such as the development stage of the medical device, the type of stakeholder involved, the expertise available, type of information required, and the resources available [2, 6, 12, 14].

The aim of this study is an illustration of how stakeholder views can be elicited, and how these views can further be weighed in the R&D decisions regarding the development of a diagnostic test (Dx) for kidney disease (KD). Second objective was to identify how stakeholder perspectives are used by manufacturers and weighed against other criteria relevant for the development of the medical device.

2. METHODS

2.1 The case study

The medical device proposed for this study is a portable point-of-care (POC) Dx that uses capillary electrophoresis with conductivity detection to determine a broad spectrum of substance concentrations in human blood and urine in less than two minutes [22]. The manufacturers envisioned the test as an easy-to-use test for the detection of sodium in urine and potassium, calcium, phosphate in blood. The study was carried-out independent but with an active participation of the manufacturers developing the POC test. This study started with the proposition that the test would have a potential for patients at risk of kidney failure (KF). In the first part of the stakeholder involvement research, stakeholders were involved in the product development – at the Targeting Product (TP) stage. At this stage, manufacturers aimed to develop a medical device that enables detection of levels of potassium in

urine. The second part was carried out before large scale testing of the Dx could start – at the Early Proof-of-Concept (EPC). In this stage, the manufacturers were testing the sensitivity and specificity of the medical device with regard to potassium detection.

2.2 Stakeholders definitions

The stakeholders in this study were divided into “users” and “key-informants”. The “users” were defined as those who have conditions and disorders that could benefit from the use of the test; e.g. patients, or those that use the device on behalf of the patients, e.g. clinicians [2, 12]. “Key-informants” were defined as those who have experience-based and/or professional-based knowledge on different aspects of the test to be developed, e.g. clinical experts, patient advocates, funding institutions and health care insurers [23].

2.3 Stakeholder involvement methods

Stakeholders opinions were explored with the use of open, semi-structured interviews and structured questionnaires. In the TP stage, a total of 40 interviews with various end-users (22 patients and seven general practitioners - GPs) and key-informants (five radiologists and six radiographers) were conducted. The convenience sample of specialists, GPs, radiographers and radiologist was recruited through snowball sampling. To prevent bias by location, the specialists were recruited across the Netherlands. The interviews with the GPs, radiologists and radiographers had a qualitative focus and were semi-structured. The interviews started with current practice in screening and monitoring of patients with kidney dysfunction and satisfaction with current care. The proposition of a POC test was outlined. The needs and wants with regard to such a test were elicited, along with perceived clinical and ease of use benefits, both from the perspective of the specialist and the patient.

A structured interview was conducted to determine the needs and wants of the patient population at risk for kidney dysfunction. A literature research was performed to determine which patient population was most at risk of KF and in which patient population a POC test would be most (commercially) viable. The literature search was performed in Medline, using the MeSH terms: diagnosis, kidney disease, nephropathy, primary care and secondary care. After analysis of the results, patients were included based on their disease, diabetes Mellitus type 2. There were no exclusion criteria based on age, race, gender or duration of the disease. A

convenience sample of patients was included just prior or after their 3-monthly check up appointment with the doctors assistant at the GP medical practice. Patients were asked for background characteristics, satisfaction with current practice, perceptions of current testing and POC testing of renal failure and their preferences for testing frequency and method using a series of open and closed ended questions. The interview was administered face-to-face by a doctors assistant at the GP medical practice. The questionnaire was pilot tested on three patients with diabetes Mellitus in different age groups. It was also verified with a doctors-assistant. Subsequently a few alterations to the questionnaire were made.

The primary exploration of stakeholders opinions in the EPC stage was conducted through an open interview with seven key-informants identified with the use of purposive sampling (one GP, one nephrologist, one pre-dialysis nurse, one Dutch Renal Patient Association representative, one Dutch Kidney Foundation representative, one insurance company representative, and one scientific researcher with experience in tele-monitoring). The interviews with key-informants were semi-structured with a framework of themes regarding their needs, wants and expectations of a home test for kidney function. Questions or themes brought up by the key informants themselves during the interviews were highly appreciated.

Secondly, patients were asked for their opinions about home monitoring of kidney function. A web-based questionnaire was developed that proposed different scenarios for home testing which varied with regard to frequency and way of contact (face to face or telephone) with the GP or specialized nurse, responsibility for acting on test results (patient, nurse or GP), cost of treatment to the patient and health benefits or using a home monitoring test. Open ended questions were used to elicit patient perceptions on ease of use of a POC test, the influence of the test on the relationship with the doctor and whether the patient felt capable and motivated to self-manage his disease. The survey ended with a series of socio-demographic questions. The end-user questionnaire was carried out with the help of the Dutch renal patient association. Through the internet panel of this association patients in a pre-dialysis stage of kidney function or in dialysis were targeted. In total 34 patients were sent the invitation for participation in the questionnaire. Next to this there was a general call on the website of the Dutch renal patient association and a call was placed on a forum for renal patients. The only inclusion criteria is that patients had to be diagnosed in any stage of Chronic Kidney Disease (CKD).

A scenario building method was used in this research to help manufacturers visualize and understand possible future alternative implementation areas for medical device under development.

2.4 Data analysis

Descriptive statistics were used for analyzing socio-demographic and multiple choice questions where applicable. Qualitative interviews were tape-recorded, analyzed and coded to put answers to questions in themes.

3. RESULTS

The first brainstorm session with manufacturers revealed that they envisioned that the detection of sodium in urine and potassium, calcium, phosphate in blood would benefit clinicians and/or patients at risk of KF, and that it could be used for daily screening of kidney functioning. In addition, the perceived benefits of the medical device according to the manufacturers were its portable nature, the quick diagnostic turnaround time, the clinical value in daily monitoring of KF, reduced hospitalization, and improved accuracy of the test compared to the current standard. Three potential implementation areas were identified, namely the use of the novel medical device: 1) at home as a self-monitoring tool, 2) as a POC test in the GPs office, and 3) as a POC test in the hospital.

The results of the literature search indicated four diseases that increase the risk of KF: Diabetes Mellitus (DM) (prevalence of 5%), hypertension (prevalence of 5%), Tubulointerstitial disease (prevalence of 0.02%), and Glomerulonephritis (prevalence of 0.006%). The application of the medical device in the two most prevalent diseases in the Dutch population was preferred by the manufacturers based on the potential market size. As the DM population has a higher risk of developing KF and a higher familiarity with self-monitoring, the initial medical device application was targeted at DM patients population (box 1).

Box 1. Current management of the DM population.

DM is a chronic disease, characterized by repeated high blood glucose levels. DM occurs in two forms, type I and type II. DM is associated with the possibility of serious complications like atherosclerosis, diabetes retinopathy and nephropathy (KF). Monitoring of kidneys function in patients with DM is important because KF is the main cause of death in insulin dependent diabetic patients [24]. In current disease management, kidney function is monitored yearly with a visit to the GP and a blood test performed in the laboratory. When DM patient is diagnosed with nephropathy, the standard procedure is to perform a medication check, give lifestyle advice, start blood pressure monitoring, plan the follow-up protocol and if necessary contact nephrologists. Current laboratory tests focus on levels of creatinine, micro albuminuria, potassium, and sodium, and calculation of eGFR.

3.1 Stakeholder involvement in the Targeting for Product (TP) stage

A structured interview with 22 patients was conducted. The majority of patients were in the age group 50-75, which is expected based on the prevalence of DM in the Dutch population, and did not suffer from KF. Patients indicated that they were very satisfied with the current standard of monitoring of KF. In general, patients were positive about the use of the medical device in the GP office. The perceived advantages of a new medical device where: more frequent tests, higher time efficiency due to less hospital visits, and more patient friendly system (small fingertip puncture instead of the vena puncture). With regard to self-monitoring at home, the majority declared that they would be willing to use the medical device at home if recommended by their family doctor, but they were unwilling to take action or unsure what action to take based on the results.

Based on the perceived benefits of the medical device described by the researchers during the interviews some GPs indicated a discrepancy between the daily use of a novel medical device as a two-minute POC test with the slowly progressive nature of KF. More frequent testing was deemed unnecessary by GPs. Moreover, the use of the test as a regular screening tool would increase their workload, and the way in which such a POC screening test would be reimbursed was unclear. All GPs saw the potential of using the POC medical device in their offices as a tool to screen patients with undiagnosed KF. However, they pointed out that the proposed medical device was not applicable as a replacement of the standard laboratory tests because it was not designed to detect creatinine, which is the most important pathological sign of KF. The GPs rejected the potential of the test to be used as a self-monitoring

tool mostly due to the threat of over-testing and false negative results that could harm the patients.

The radiologists and radiographers all agreed that the new medical device could be used in the hospital laboratories or radiology departments, but they did not see clear additional benefit to the current testing in terms of clinical need (a faster diagnoses would not change their actions or change patient outcomes in case of KF) or financial benefits. Only in the case of urgent computed tomography scans (CT scans), e.g. in case of suspected aorta dissection or pulmonary embolism (PE) they felt that a quick test of KF would allow for direct actions (e.g. drinking lots of fluids after the scan) that would benefit the outcomes for the patient. Table 1 presents the summary of the interviews results.

Based on the results of the interviews six different implementation scenarios were developed. Scenarios differed in location (radiology department, hospital laboratory), population (acute, semi-acute and scheduled patients), and clinical example (aorta dissection, PE or abdominal scan). The potential users of novel medical device selected to participate in this part of the research were radiologists (n=12) and radiographers (n=30).

Table 1. Results of the users interviews: TP stage.

	Patients home (SM¹)	Primary care - GPs office (S²,M³)	Secondary care – hospital laboratory/ radiology department
Clinical need	Low, because of the slow disease progression;	Low, because of efficiency and quality of current laboratory test and no recognized clinical benefit in more frequent testing;	High, in the case of CT with contrast agents;
Market size	Patients at high risk of or with existing kidney dysfunction;	Patients at high risk of or with existing kidney dysfunction;	Patients at high risk of or with existing kidney dysfunction;
Users willingness to accept	Yes, if GPs will recommend it;	Yes, as a tool for early identification of decreasing kidney function patients;	Yes, as a tool for identification of kidney dysfunction patients;
Professionals⁴ willingness to accept	No, due to threat of over-testing and false-negative results;	Yes, only as a full replacement of laboratory tests;	Yes, as an additional laboratory test for patients before CT scan;
Barriers	Patient age limits ability to operate medical device; No reimbursement possibilities; Satisfaction with current tests management; Low willingness of patients to take the disease management responsibility; Reluctant position of GPs;	Workload threat; Not a replacement of current laboratory tests; High costs of the medical device; No reimbursement possibilities;	Costs higher than current laboratory costs; No reimbursement possibilities; Not a replacement of current laboratory tests;
Facilitators	Positive attitude towards medical device; Growing trend of disease self-management; Patient friendly (small puncture in the fingertip instead of vena puncture); Time efficient;	Patient friendly (small puncture in the fingertip instead of vena puncture);	Patient friendly (small puncture in the fingertip instead of vena puncture); Time efficient;
Medical device design requirements of users	Good feedback system on the tests results; Reliability of the measurements; Handy and easy to use medical device;	High reliability of tests results; More measurements possible; Easy to use; Low maintenance; Quick results (<5min); Small and handy; Automatically stored data; Sufficient sustainability of chips with long shelf-life.	More measurements possible; High reliability of tests results;

¹SM – self-monitoring, ²S – screening, ³M – monitoring, ⁴GPs, radiologists, radiographers

The respondents were asked for the perceived benefit of having a POC test for each scenario. The results showed that a test for KF was seen as beneficial only for the semi-acute patients undergoing CT screening. The immediate health benefits to the patient and the reduced time investment were seen as the greatest benefits from a patient perspective. POC screening of kidney function would omit the need for the patients to make an additional hospital visit to test KF prior to the scan. The implementation scenario in box 2 was proposed as the most viable way forward for the development of the medical device.

Box 2. Detailed implementation scenario for use of POC medical device in the hospital laboratory.

A POC medical device is present in the hospital laboratory. It is used for blood measurements of semi-acute patients with possible PE. When PE is being suspected, a number of blood tests are done, in order to exclude important secondary causes of PE. This includes also some screening tests for renal function. If the results of the blood screening are abnormal, further investigations might be warranted. The measurements data is automatically streamed, transmitted and automatically formatted in the patients file. The results of the tests can be discussed during a consultation with the doctor. The tests with the new medical device are faster, more reliable and less painful than currently performed tests.

In the final brainstorm session in the first stage of the research, the manufacturers dismissed the use of medical device as recommended in the implementation scenario because of two reasons: 1) it would be impossible to provide the test in a competitive price range compared to those in the hospital laboratory, and 2) the estimated market size was considered too small.

3.2 Stakeholder involvement in the Early Proof-of-Concept (EPC) stage

The stakeholder involvement was continued in the EPC stage of medical device development. At this stage the manufacturers had added the detection of creatinine in blood to their intended medical device design, although they still had to provide proof-of-concept for potassium. The first brainstorm session with the manufacturers team revealed that the manufacturers decided to continue with further development of their medical device as a self-monitoring POC application for patients at risk of CKD (box 3). CKD is a condition with a prevalence of 0.1% to 5.3% (depending on the stage of the disease) and an incidence of 0.3 to 1.2 per 1000 patients per year.

Box 3. Current management of the CKD population.

According to the data presented by the Dutch Kidney Foundation the number of Dutch people with KD is estimated at around 60,000 and it is still increasing. There are about 6,000 people on dialysis and approximately half of the patients in dialysis centers are 65 years or older [25]. CKD often only leads to complaints in later stages. Patients find it very difficult to adhere to a treatment, when they have only minor complaints, which makes following right diet and timely and adequate monitoring of CKD at this moment difficult. In 2010 the Dutch Health Council investigated the research needs of patients with CKD, and they indicated that there is a need for measurement instruments at home. The patients seek an instrument which can relate their blood values to their kidney function. This enables them to detect changes in the blood values and adjust the medications and diet in an earlier stage. This need for measuring kidney function at home did not make it into the top three for the research agenda, but was seen as a relevant topic [26].

During the second brainstorm session with the manufacturing team the CKD stage-III population was selected for further analysis because of its high prevalence in the population and the fact that in this stage most patients are already identified and thus the implementation of the disease self-management program would be possible for that population. The use of the medical device as a screening test for patients yet to be identified (CKD stage I and II) was dismissed because other cheaper screening tools were available on the market and the novel medical device would not be able to compete with them. Two potential implementation areas for the novel medical device for the CKD stage-III population were proposed: self-monitoring by patients at home and patients monitoring at their GPs office.

The interviews with key stakeholders revealed that there was no perceived clinical need in applying the medical device at the GPs offices, and that the only perceived gap in care was related to self-monitoring, because of the increasing interest in involving patients in their own care [27, 28]. However, self-monitoring raised the issue of patients' ability, willingness and responsibility to perform self-care. The nephrologist stated that patients should take the responsibility for using the medical device and acting on information on themselves, with the remark that not all patients are actually able to do so.

“Some patients are very qualified to check their own health, they suggest changes in treatment and provide feedback. Those patients shall feel more empowered by taking the kidney function test at home, they have more control over their disease and are less depending on doctors. Other patients

will barely understand what I just have said about their condition and treatment.” (nephrologist)

Other key-informants also agreed that it might be too much responsibility for patients to handle, especially if they will also have to act on results. They agreed that the doctors should remain responsible for reading and acting on results of any self-monitoring test performed.

“When a patient has a deviant test, I first would like to see him during consultation hours. Everything should be questioned, fevers, diseases etc. You cannot simply rely on measurements, a direct refer to the nephrologist is not possible. The nephrologist expects from me that I investigate the cause of the deviation. A patient should also be seen on a regular basis even if they have no deviant test. For the doctor it is necessary to see the patient to get a general impression of the health status of the patient.” (GP)

There was a resistance of the majority of key-informants to reduce the extent of contact between patient and doctor, which diminishes some of the potential financial benefits of using the medical device. The nephrologist also stated that the frequency of testing should be based on course of the disease, not on the ability of the medical device. Indeed, other key-informants agreed that there was no need to increase the test frequencies for CKD patients. The interviews also revealed that for the self-monitoring application to succeed, the medical device must fit within an existing care program, which means that it should be implemented in a wider self-management care program. Furthermore, it should be supported by clinicians and nurses, as they would have to be the ones to suggest the medical device to patients and motivate them to use it.

All key-informants stressed the need for training the patients who are going to test their kidney function at home, and that such self-monitoring medical device should be reimbursed. However, the insurance company representative revealed that within the current reimbursement schemes there is no such possibility for reimbursement.

“In self-monitoring it is important that there is exchange of views among kidney patients. Main problems can be collectively discussed and solved. A group training is an ideal opportunity to meet other motivated kidney patients.” (nephrologist)

“Patients should have a choice between a group or an individual training. My opinion is that an individual training or an extra consultation can be an option for patients with a lower education level or older patients.” (dialysis nurse)

Table 2 presents the summary of the interviews results.

Table 2: Results of the key-informants interviews: ECP stage.

	Patients home (SM¹)	Primary care - GPs office (M²)
Clinical Need	Low, because of the slow disease progression;	Low, because of efficiency and quality of current laboratory test and no recognized clinical benefit in more frequent testing;
Market size	Patient age limits ability; Patients with diagnosed CKD – pre-dialyzed and dialyzed;	Patients with diagnosed CKD;
Users willingness to accept	Yes, if GPs will recommend it;	Yes, as a tool for testing kidney function in patients with diagnosed CKD;
Professionals willingness to accept³	No, due to threat of over-testing and false-negative results;	Yes, as a replacement laboratory tests;
Facilitators Implementation	Growing trend of disease self-management;	Costs (to GP!) lower than laboratory tests;
Barriers Implementation	Low willingness to decrease contact moments with doctors; Providing training is essential; Low willingness to give the disease management responsibility to patients; No fit with current disease management; No reimbursement possibilities;	Costs higher than current laboratory costs; No reimbursement possibilities;
Medical device design requirements of users	Warning signal if measurements are not correct; Reminder message/alarm; Automatic data entry; Automatically stored data; Easy to use;	High reliability of tests results;

¹SM – self-monitoring, ²M – monitoring, ³GPs, nephrologists

The results of the key-informants interviews conducted in step two of the research were discussed with the manufacturers team during another brainstorm session. The implementation areas were re-defined and four initial implementation scenarios for self-monitoring CKD stage-III patients at home were developed. The scenarios differed with the levels of self-monitoring responsibility, amount of contact moments with doctors and reimbursement schemes.

The initial implementation scenarios were evaluated by the patients through the web-based questionnaire. The final sample contained 17 patients. They were balanced in gender (53% women), with a mean age of 37.8 years, and on average 12 years diagnosed with CKD. All patients reported medium (52.9%) or higher education (47.1%), no lower or uneducated patients entered the questionnaire. The sample was heterogeneous with regard to the stages of CKD (Stage I-III – 35.4%, stage IV pre-dialysis – 29.4% and stage V dialysis – 35.3%). The questionnaire started with a short description of the new medical device, and the presentation of four scenarios. Subsequently a number of open and closed questions were asked.

The results showed that 82% of patients reported the willingness to test their kidneys function with POC at home. They saw the possibility to gain more insight in the functions of their kidneys, to control the disease development and to decrease the number of contact moments with doctors. The opinion on higher frequency of the tests were divided, as some patients thought it was not really needed, while others saw the added benefit in faster detection of kidneys deterioration, which would allow them to anticipate faster, prevent complications and save costs. However, patients stressed that because the direct insight in the test results would be of high importance for them, they must be presented in a clear and understandable form. They also reported that in the case of the deviant test results they would like to have a possibility to contact doctor themselves instead of waiting for the POC system to do it instead. No clear directions were given about the preferences for the training that would be required to use novel medical device. The results of the patient questionnaire combined with the information gathered from the key-informants interviews were presented in a form of a detailed implementation scenario (box 4).

Box 4. Detailed implementation scenario for CKD patients monitoring at home.

The main aim of the self-monitoring is to slow the progression of the CKD. The patient has a POC medical device at home to measure sodium in urine and potassium, calcium, phosphate and creatinine in blood. The patient does not have to travel to have the measurements taken and wait for a long time for the results. The patient has followed an extensive individual training given by nurse on how to use the medical device at home and how to interpret and act upon the results. The patient measures kidney functions more often than it is measured by the current standard. If the data are not transmitted at the scheduled time, the unit beeps an audible warning, and a digital voice reminds the patient to perform tests. When a test is deviant, the patient has a responsibility to contact the specialist. Besides this the data is automatically streamed and transmitted and automatically formatted in the patient files. The results of the tests can be discussed during a consultation with the doctor. The amount of contact moments with the doctor does not change in the beginning of the self-management program, but the patient can indicate if he or she wants less contact moments. The patient seems more involved in the self-management of own KD, which increases the effectiveness of the treatment and leads to a delay of the deterioration of the kidney function.

In the final brainstorm session the manufacturers agreed that the fit between the potential of a CKD test and the current trends of self-monitoring and self-management is an important driver for them for further development of medical device.

4. DISCUSSION

The aim of this research was to define the clinical need for a POC Dx using iterative stakeholder analysis. This study has implemented a structured approach to stakeholder assessment, including an exploratory phase, a validation phase and an in-depth and systematic review of the epidemiological and clinical literature. Based on that it has been possible to define different scenarios in a qualitative way, that directed the discussions and brainstorm sessions with the device manufacturers.

This study showed that stakeholder involvement can be a useful instrument for the manufacturers to identify new clinical markets and implementation barriers for new medical devices, even in an early stages of development. The analysis also created awareness of a range of implementation issues that could potentially impact the design, the functionality and actual use of the device. Another finding is that it is essential to have the manufacturers actively involved in the brainstorm sessions that

were held throughout the whole process, as this helps them understand the ratio behind the different steps. Interestingly, a number of potentially conflicting arguments arose during the stakeholder assessment such as those between market size and commercial viability on one side and the patient needs and clinical usefulness on the other.

There are several reasons that determine the success of stakeholder involvement. First, the size of the company and the product portfolio do impact the use of stakeholder input. It is assumed that small-sized companies carrying single products or Intellectual Property are more strongly pushing the technology itself. Previous research has shown that it is hard to convince manufacturers to change the direction of medical device development when it is generally dominated by technological abilities [14, 29].

Second, it is imperative that the initiative to perform an analysis of the stakeholder involvement has to come from the manufacturers or informal investors demanding such input. If not, it is likely that stakeholder involvement is viewed as an isolated part of the project that is not matched with the product development itself. It is possible therefore that cognitive biases, specifically confirmation bias, may have affected the interpretation of results. This kind of bias where decision makers search for or interpret information in a way that confirms their hypothesis, and ignore the evidence that contradict it, is a widely recognized phenomenon [30, 31].

A third important factor is that the company representatives responsible for ordering or conducting the stakeholder involvement research should have sufficient decision power in order to disseminate the research results and to make sure the actions are being taken within the company that follow research recommendations [7, 13]. It is possible that the team conducting research presented in this paper did not have enough power within the company to disseminate the results of the stakeholder involvement analysis and influence the POC Dx development.

However, it is possible to further improve the methods of stakeholder involvement. In this study it was deliberately chosen to carry out interviews, because of the flexibility to modify questions during the interviews itself, and also to tailor the interviews to the specific stakeholder. In addition, the questionnaires were chosen to facilitate the recruitment of a larger number of stakeholders. However, these closed-format questionnaires are less favorable to explore stakeholder views qualitatively. Especially when the research is conducted in the early phases of the medical device development, open interviews are preferred. Another issue is that the questionnaire

were completed by more educated and more technically skilled patients that were more comfortable with participating in an online forum and filling in the web-questionnaire. The researchers acknowledge that this may have biased the results, and recommend interviews as a primary assessment method.

5. RECOMMENDATIONS FOR IMPROVING STAKEHOLDERS ENGAGEMENT

1. Stakeholder engagement should be part of the R&D cycle and commissioned in order to inform the product development, and allow systematic evaluation against business and commercial prospects.
2. Stakeholder involvement should ideally be supervised by an internal company researcher, to guarantee the results are seen as part of the product development strategy, and to avoid that the stakeholder involvement is seen as an external justification.
3. In addition to performing stakeholder involvement analysis, it is recommended for the company to also have a direct interaction with stakeholders, especially future users of their medical technologies, rather than merely being informed about them through intermediaries.

6. CONCLUSIONS

Stakeholder involvement analysis alone has only limited ability to change the manufacturers concept and objectives in medical device development. Other forces, i.e. existing and/or potential funding, and the size of the target population appear to be important drivers as well. Future studies should aim to link early indicators of medical device success, as perceived by clinical stakeholders, to its actual implementation. The inclusion of iterative stakeholder involvement into the medical device development must therefore be an integral part of the device development.

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Chapter 5: Commercial Viability of Medical Devices Using Headroom and Return on Investment Calculation

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ABSTRACT

Background: The market success of a medical product depends on its commercial viability, yet this may be hard to predict during the development process of medical devices. This paper aims to determine if applying the Headroom method combined with Return on investment (ROI) analysis allows for estimation of the potential commercial viability of one therapeutic and five diagnostic devices.

Methods: The devices were targeted at different disease areas. Information regarding the maximum additional health benefit that could be obtained with the new device, the estimated production price and expected sales volume was gathered from literature and expert opinions. A willingness-to-pay threshold for one additional Quality-Adjusted Life Years of €30,000 was assumed for Headroom calculation.

Results: The analysis showed that the device with the highest estimated headroom per unit was RAPAI: a computed tomography photo-acoustic instrument for imaging inter-phalangeal joints (€1,645,120), followed by CBPM: continuous blood pressure measurement device (€922,440), Home Brain Monitoring (HBM) device (€750,000), a portable point-of-care (POC-CKD) device (€36,250), and the IHP: injectable healing plasters (€22,100). The devices with the highest estimated ROI were RAPAI (€14,951,200), and POC-CKD (€14,100,000), followed by HBM (€9,450,000), CBPM (€8,624,400), and IHP (€7,050,000). Overall, RAPAI is expected to have the highest potential commercial viability and HBM and IHP the lowest.

Conclusions: The presented combined method is feasible, useful, and informative to help assess the potential commercial viability of medical devices under development. It might be an answer to the growing need of performing value-based pricing of devices replacing currently dominating cost-plus pricing approach.

1. INTRODUCTION

The success of a medical device for manufacturers is determined by its commercial viability, i.e. the ability of a device to compete effectively on the market and generate sustainable revenues. As such, an estimation of the expected net revenues will usually drive the initial investment decisions and influence the development and market access strategy [1]. The value of a medical device to society is commonly determined by its benefits in terms of health outcomes compared to usual care or another device; in other words the opportunity it provides to generate value to patients and to the wider society [2-4]. The investment and design decisions regarding medical devices influence the prospects of their commercial and societal value. They should thus be supported early in the device development process [5].

An initial economic evaluation can help manufacturers to structure the evidence on potential effectiveness and costs of their technology compared to current care, and to identify stakeholders involved in the development process, together with the key value drivers of the technology [5]. Ideally, economic evaluations should begin with a ballpark estimation of potential cost-effectiveness of medical device at an early stage of the development, and continue with a more detailed analysis as the development progresses [3, 5, 6].

Traditional health economic evaluations of medical devices are well developed in the context of mainstream Health Technology Assessment (HTA), mostly to inform reimbursement decisions by regulatory agencies or a national health service at the time of market launch [7, 8]. The evaluations usually compare the new and alternative intervention in terms of their costs and consequences, e.g. cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost-benefit analysis (CBA). Early stage health economic evaluations differs from this, as they aim to support decisions on allocation of the research and development (R&D) resources from a business perspective in early product development stages. These evaluations intend to assess the likelihood that the expected returns will outweigh the likely costs for the company. Typical methods to quantify developmental uncertainties and inform investment decisions are the Real Options Analysis (ROA), the rudimental analysis of costs, and the Return on Investment (ROI) [9]. The ROA method is based on the option valuation techniques to capital budgeting decisions [10]. In the rudimental analysis of costs, manufacturers combine all the costs associated with a medical product, to evaluate whether there is potentially a cost saving to be generated by the new medical device compared to current practice [8, 11]. Finally, a ROI calculation aims to determine if new device has the potential to bring (long-term)

profits to the company and thus indicates the development feasibility [12]. These methods, however, are neither well documented nor fully exploited to inform product development decisions by the medical device industry [3, 4, 13, 14].

Recently, the Headroom method has gained interest within the medical device industry as it considers the uncertainty surrounding investment decisions from a business perspective, as well as the expected additional value of a product for society. The method can thus provide manufacturers with a range of potential target sales prices for the device, based on the added value produced to society, instead of the cost-plus approach that prevails in traditional business planning. Furthermore, the target sales prices can be used to estimate the ROI for the company. This relatively low data- and analytic demands of the Headroom and ROI methods are likely appealing to small and medium sized companies (SMEs) in the medical device industry, that need to assess their products within the constraints of limited resources [9, 12]. However, as the existing Headroom method hinges upon the maximum achievable health benefit that would be gained by resolving all disutility of a given disease, it only provides a theoretical upper bound for a products added value. Therefore, the Headroom approach in the presented study is adapted to consider the most realistic approximation of additional health benefit, as can be derived from literature and interviews.

The aim of this paper is to determine whether the adapted Headroom method combined with ROI can be used to determine commercial viability of a range of medical devices and support go/no-go investment decisions at the early stages of the devices development.

2. METHODS

2.1 Theoretical underpinnings of the Headroom and ROI methods

The Headroom method, coined as such in 2007 [12], was first described as the Effectiveness Gap Method in 1997 by Sculpher, Drummond and Buxton [6]. It was then suggested as a part of an early stage iterative economic evaluation of HTA process. The Headroom method starts with the calculation of an effectiveness gap, which can be expressed in Quality-Adjusted Life Years (QALYs), i.e. a measure that takes into account the quantity of life expressed in years, in terms of survival or remaining life expectancy, and the health-related quality of life measured by health utilities [4, 5]. The Headroom method may be used to estimate a maximum

reimbursable price for a medical device that can be justified by the cost/QALYs threshold. This threshold varies between jurisdictions but typically falls between €20,000 and €35,000 in Europe. By comparing the maximum reimbursable price to the expected production costs and desired commercial sales prices, the viability of the medical product can be estimated [15]. Based on the results of the headroom calculation, the manufacturers may decide to proceed with the development of a new device if its expected unit production and operating costs are lower than the anticipated headroom. When the headroom is insufficient this may justify a recommendation to stop further development and channel the investment to other devices in the portfolio, that are more likely to produce societal value [16]. Based on the National Health Service (NHS) uptake of 14 medical devices evaluated with the use of the Headroom method, the sensitivity of the Headroom method is reported to be 92 percent (which is the percentage of devices with a favorable headroom that achieved NHS uptake), with a negative predictive value of 67 percent (percentage of devices with an unfavourable headroom that was not taken up by the NHS) [17].

The disadvantage of the traditional Headroom method is that it relies strongly on the assumption that the incremental benefit of using a new medical device can be as large as to attain perfect health [12, 18]. Although there is only little data available on estimated incremental costs and effects in the early development stages, it was decided to approach the headroom calculations as realistic as possible by taking a best approximation of a device's expected incremental effectiveness. The headroom calculation was discontinued if there was an indication that the new device would not be more effective than its comparators on the market or that it would be an equivalent to the current alternative on the market, i.e. the same intended use and/or technological characteristics, and no improvement of safety or effectiveness [19]. In the case of a substantially equivalent device, the benefit of introducing new device are on the costs side, and thus the Headroom method can be replaced by the standard cost-minimization approach [12].

Whereas the headroom basically links the societal value of the device to the additional cost that is justified to pay for that value, the ROI analysis aims to measure the rates of return on investment in an economic entity. It originates from business economics, and informs business planning and investment decisions in medical technology development [4, 9]. It is thus a base to compare different project investments [20]. In this approach, ROI can be estimated using the headroom, the likely device production cost and expected sales volume, discounted over the time horizon of device use [12].

2.2 Study design

This research adopted a case study approach. Six medical devices which were funded within one funding scheme instigated by the regional government to stimulate economic growth in the Twente area in the Netherlands were selected for analysis. As at the time the aim of the regional government was to further invest in the most viable approaches, it was relevant to both the manufacturers and the regional government to have insight in the commercial viability of these medical devices.

The analyses of each case study started with a qualitative open face-to-face interview with the team of device manufacturers. Each team consisted of the project leader and/or an engineer or an entrepreneur within the medical device company/research group. There were usually between one to three persons interviewed within the team. Each team was interviewed two to four times. The information gathered during the interviews was used to (1) understand the characteristics of new device, (2) determine the perceived target area of new device (the precise aim of the new device in diagnosis/monitoring or treatment of disease), (3) analyse the potential comparators within that target area, and (4) understand the extent to which it was plausible that novel devices may offset the limitations of current alternatives without introducing new hazards (e.g. side effects). Detailed notes were taken during the interview. Further data was collected from the literature and supplemented with the consultations with experts in relevant medical fields. Figure 1 presents the study design as applied in this research and its fit to the early development stage decision context.

Fig. 1. The study design applied in this research and its fit to the early development stage decision context.

The Headroom method started with an analysis of the effectiveness gap. At this point, the substantial equivalent devices were excluded from further analysis, because of the comparable effectiveness (i.e. no effectiveness gap could be demonstrated). For the medical devices that appear to have headroom based on their effectiveness gap and marginal costs, and for which further development and investments based on the business case analysis seemed justified, the ROI analysis was performed.

2.3 Case Studies

The devices used as case studies in this research covered a variety of disruptive and incremental innovations ranging from supplies to therapeutic or diagnostic devices. The main target application, device type, innovation type, and stage of the development of each case study device are described in table 1.

2.4 Analyses

2.4.1 Headroom Analysis

The health utilities used to calculate the effectiveness gap ($\Delta QALY$) were expressed by the Health-Related Quality of Life (HRQoL) estimates, where 1 signifies perfect HRQoL and 0 represents death. $\Delta QALY$ was thus estimated as a function of improvement in HRQoL due to the use of new device, i.e. the difference between the effectiveness of the current treatment (HRQoLCT) and the effectiveness of the treatment with the use of new device (HRQoLND), and the duration over which this improvement is sustained, represented by t – time in years (equation 1):

$$\Delta QALY = (HRQoLND - HRQoLCT) \times t = (\Delta HRQoL) \times t$$

$\Delta QALY$ was further converted into monetary terms to offset the financial costs of the novel devices, and to present the “net maximum cost” for each device [21]. A willingness to pay (WTP) threshold of €30,000 for one additional QALY was assumed for the headroom analysis. This represents the societal WTP for one unit of health benefit (1 QALY) [22]. An additional estimated savings (ΔC) due to replacing current treatments/technologies with the new devices were also included, and thus the headroom per patient ($\max \Delta \text{CostPP}$) was estimated as (equation 2):

$$\max \Delta \text{CostPP} = (\Delta QALY \times \text{€}30,000) + \Delta C$$

Table 1. The Main Target Application, Device Type, Innovation Type, and Stage of the Development of Each New Device under Development

Device	Target application	Device type	Innovation type	Development stage
The Injectable healing plasters (IHP)	Innovative treatment for cartilage defects healing. Its biggest advantage is using gel components of natural origin that match those of the damaged cartilage tissue, providing biocompatibility and biodegradability for new tissue formation.	Therapeutic	Radical	First clinical trials
A portable point-of-care device (POC-CKD)	Device that could enable patients diagnosed with stage III chronic kidney disease (CKD) to self-manage their CKD at home in a fast and effective way through measurements of 5 substances: sodium in urine and potassium, calcium, phosphate, and creatinine in blood.	Diagnostic	Radical	Prototype development
Continuous blood pressure measurement device (CBPM)	Device that could provide more accurate blood pressure measurements together with other parameters (e.g. peripheral resistance) for haemodialysis patients in the 48-hour ambulatory use, and in the hospital environment.	Diagnostic	Incremental	Proof of principle
A computed tomography photo-acoustic instrument for imaging inter-phalangeal joints in the hand (RAPAI)	Device for an early rheumatoid arthritis (RA) diagnosis and therapy monitoring. It is destined for the implementation in the hospitals, and in the future also in the outpatient clinics and rapid/urgent-care clinics.	Diagnostic	Incremental	Targeting for specific product
The flexible endoscopy robot (FLEX)	Device designed to support large scale screening programs for colorectal cancer. It combines diagnosis with small interventions (e.g. removal of polyps) in the form of easy manoeuvrable light weight device that ergonomically fits in the intended working environment. The idea behind using this robot is to increase the efficiency both in speed of the procedure as in the number of staff needed during the procedure and their level of specification.	Diagnostic	Incremental, add-on	Proof of principle
Home Brain Monitoring device (HBM)	Device developed as an alternative to routine diagnostics for patients evaluated for epilepsy. The idea behind it is to further improve sensitivity of Electroencephalography (EEG) records through long-term EEG recordings (24-48h) that increase the chance of detecting epileptiform abnormalities. Besides the advantage of being able to measure for a longer time, new device is expected to be more comfortable for patients to measure EEG at home instead of inpatient recordings, as it is small and easy to wear for patients.	Diagnostic	Incremental, add-on	Prototype development

To estimate the headroom per device unit ($\max\Delta\text{CostDU}$) $\max\Delta\text{CostPP}$ was multiplied by the potential number of patients (N) per device unit per year, and it was estimated as (equation 3):

$$\max\Delta\text{CostDU} = \max\Delta\text{CostPP} \times N$$

The rudimental analysis of total costs (C_{total}) for each particular treatment the new medical devices were targeted at, based on the direct (C_{direct}) and indirect costs (C_{indirect}) calculation, was performed to analyse the cost margin of new devices (C_{margin}) with the use of the $\max\Delta\text{CostDU}$ and N (equation 4):

$$C_{\text{margin}} = \max\Delta\text{CostDU} - (C_{\text{direct}} + C_{\text{indirect}}) \times N = \max\Delta\text{CostDU} - C_{\text{total}} \times N$$

2.4.2 ROI Analysis

The ROI was estimated as a function of the $\max\Delta\text{CostDU}$ with the inclusion of the estimated cost of the medical device development (CDD) and expected sales volume (V) in the first year of the device implementation (equation 5). CDD was estimated by the manufacturers per device unit based on the estimated R&D cost and the cost of device manufacturing.

$$\text{ROI} = (\max\Delta\text{CostDU} - \text{CDD}) \times V$$

3. RESULTS

3.1 Case Studies: Preliminary Analysis of the Clinical Conditions

The preliminary analysis of the clinical conditions revealed that six case studies devices target five different diseases. The prevalence of those diseases ranges from 0.01% for chronic kidney disease stage IV/V, to 14.2% for osteoarthritis. The incidence ranges from 0.0007% for epilepsy, to 1.9% for osteoarthritis. The long-term benefits of using case study devices are accrued from either delaying disease progression, or earlier/more accurate diagnoses (which is assumed to result in earlier, more effective treatment). The expected economic benefits include many factors, e.g. shorter rehabilitation, less surgery procedures and complications, reduced costs due to better dosage of anti-hypertensive agents. The comparators of the selected devices are all standard well-established technologies/ procedure, e.g. micro-fracture for osteoarthritis or standard blood/urine laboratory tests for kidney

disease. The context of use of the devices is either hospital or patients at home. Finally, the intended users are mainly medical specialists or patients. Table 2 summarizes the main characteristics of six medical devices taken as case studies in this study.

Table 2. The Overview of Six Case Studies Used in the Research

Disease targeted	IHP	POC - CKD	CBPM	RAPAI	FLEX	HBM
	Osteoarthritis due to cartilage damage	Chronic kidney disease stage III	Chronic kidney disease stage IV/V	Rheumatoid arthritis (RA)	Colorectal cancer	Epilepsy
Prevalence of target disease	14.2% [37]	0.53% [38]	0.01% [38]	1% [39]	11.5% [40]	0.05% [41]
Incidence / year of target disease	1.9% [37]	0.12% [38]	0.03% [38]	0.03% [42]	0.04% [43]	0.0007% [41]
Long-term health benefits	Avoidance or delay in the OA development.	Delay of CKD progression.	Avoidance of hypotensive crisis.	Early diagnosis and delay of severe RA development.	Improved colorectal cancer screening that leads to early diagnosis/treatment.	Major improvements in the epilepsy diagnostic accuracy and efficiency.
Expected economic benefits	Shorter rehabilitation, less surgery procedures and complications, less hospital days.	Less laboratory tests, less visits at general practitioners office, less leave days.	Reduced costs due to better dosage of anti-hypertensive agents, less adverse health events that lead to hospitalizations.	Reduced costs due to early diagnosis of RA, tailored treatment, less visits at GP/ rheumatologists office.	Improve in colonoscopy capacity: less medical staff (also specialists) needed during procedure, decrease in the colonoscopy time (by 40%), less complications.	Eliminated visits at Lab Tech/EEG due to use of the device at home, limited visits to EEG review, and limited meetings with neurologist to 2 per year.
Competitor treatments	Microfracture, Mosaicplasty, ACL.	Standard blood/urine laboratory tests.	Standard single blood pressure measurements.	The blood measurement and X-ray.	Standard colonoscopy procedures.	Standard electroencephalography (EEG).
Intended use in	Hospital	Patients home	Patients home	Hospital	Hospital	Patients home
End user(s)	Orthopaedic surgeons	Patients	Patients	Rheumatologists and radiologists	Gastroenterologists or gastrointestinal surgeons	Patient

3.2 Headroom Analysis

The headroom and ROI was estimated for five out of six devices (IHP, POC-CKD, CBPM, RAPAI, and HBM). FLEX, which is being developed as an add-on system to the currently used endoscopes, was excluded from further calculation as it is a substantially equivalent device. Table 3 presents the input data used to feed the Headroom method and ROI analysis. Table 4 presents the output data results of the Headroom method and ROI analysis.

Table 3. Comparison of the Input Data of Five Medical Devices under Development

	HRQoL _{ND}	HRQoL _{CT}	t	C _{direct}	C _{indirect}	C _{total}	ΔC	N	C _{DD}	V
IHP	0.51 [44-46]	0.37 [44-46]	5*	€3,980 [11, 47]	€8,000 [11, 47]	€11,980 [11, 47]	€1,100 [11, 47, 48]	1	€8,000*	500*
POC - CKD	0.77 [49, 50]	0.53 [49, 50]	5*	€154 [51-53]	€180 [51-53]	€334 [51-53]	€250*	1	€1,000*	400*
CBPM	0.53 [49]	0.4*	5 [54]	€2,361 [55]	€1,200 [55]	€3,561 [55]	€3,561 **	40***	€60,000*	10*
RAPAI	0.84 [23]	0.58 [23]	10 [24]	€3,288 [56]	€240 [56]	€3,528 [56]	€4,256 [56]	20***	€150,000*	10*
HBM	0.89 [25, 26]	0.49 [25, 26]	1*	€831 [43]	€340 [43]	€1,171 [43]	€3,000 *, ** [57]	50 [58]	€120,000*	15***

*assumption based on authors and/or manufacturers estimations

**estimation of experts

Table 4. Comparison of the Output Data of Five Medical Devices under Development

	ΔHRQoL	ΔQALY	$\text{max}\Delta\text{Cost}_{\text{pp}}$	$\text{max}\Delta\text{Cost}_{\text{DU}}$	C_{margin}	ROI
IHP	0.14	0.7	€22,100	€22,100	€14,120	€7,050,000
POC - CKD	0.24	1.2	€36,250	€36,250	€35,916	€14,100,000
CBPM	0.13	0.65	€23,061	€922,440	€780,000	€8,624,400
RAPAI	0.26	2.6	€82,256	€1,645,120	€1,574,560	€14,951,200
HBM	0.40	0.40	€15,000	€750,000	€691,450	€9,450,000

The calculation of ΔQALY showed that the medical device with the highest expected increase in effectiveness compared to the current care was RAPAI. The ΔQALY for RAPAI was estimated with the use of the assumed utilities of 0.84 for mild RA and 0.58 for severe RA, based on the numbers extracted from the literature [23]. In addition, as the possibility of developing RA increases with age and the average age of RA patient is estimated to be around 75 years old it was assumed that the duration of the RA development delay lasts on average around 10 years [24]. And thus the increase in QALY was estimated as: $\Delta\text{QALY} = 10 \times (0.84 - 0.58) = 2.6$ quality adjusted life years. The device with the smallest estimated ΔQALY was the HBM. The utility of seizure-free epilepsy state of 0.89 was used in the analysis together with the seizure reduction state utility of 0.49, based on the numbers extracted from the literature [25, 26]. Furthermore, ΔQALY for HBM was estimated based on the assumption that use of the device would result in earlier diagnosis (up to a year), but not better treatment after diagnosis. ΔQALY was thus estimated as: $1 \times (0.89 - 0.49) = 0.40$ year in perfect health.

The highest additional savings due to the change of the current treatment to the use of the new device was estimated for RAPAI device: $\Delta C = €4,256$. It was calculated based on the estimated difference in costs between the treatment of mild (early diagnosis) and severe RA (late diagnosis) per patient per year [28]. The lowest additional savings were estimated for POC-CKD device that is intended to be used at home for the CKD stage III patients monitoring. That result was based on the fact that the monitoring of CKD stage III patients is based on the inexpensive laboratory tests which usually are performed twice per year. The ΔC calculation based on the list of the diagnostic costs extracted from the literature, and the additional savings per patient per year was estimated to be equal to €250. Figure 2 presents the comparison of the effectiveness gap (ΔQALY) for the five devices and estimated cost savings (ΔC) due to the change from the current treatment to the use of new device under the chosen WTP threshold for one additional QALY of €30,000.

The headroom analysis calculation per patient per year showed that RAPAI had the highest target sales price, when assuming that the incremental health benefit, as

monetized by the WTP for one QALY, plus the potential cost-savings would fully be recouped by the manufacturer in the sales product price. With an estimated Δ QALY of 2.6 and Δ C per patient per year equal to €4,256, the total headroom was estimated as: $\max\Delta\text{CostPP} = (\text{€}30,000 \times 2.6) + \text{€}4,256 = \text{€}82,256$. The manufacturers together with the experts also assumed that new imaging device will be used to diagnose and monitor around 20 RA patients per year, so the headroom per unit was further estimated as: $\max\Delta\text{CostDU} = 20 \times \text{€}82,256 = \text{€}1,645,120$. The lowest potential commercial viability was estimated for HBM. Based on the assumption that Δ C per patient per year was equal to €3,000, and the estimated Δ QALY of 0.4, the headroom per patient per year was equal to: $\max\Delta\text{CostPP} = (\text{€}30,000 \times 0.40) + \text{€}3,000 = \text{€}15,000$. With the additional assumption that the number of patients that will use the device per year will be equal to 50 the headroom per device unit was further estimated as: $\max\Delta\text{CostDU} = \text{€}15,000 \times 50 = \text{€}750,000$. The lowest target sales price was estimated for IHP. Δ QALY calculation was based on the utilities extracted from the literature: for the mild OA equal to 0.51, and for the severe OA equal to 0.37, and also an assumption that the benefits of using IHP are extending over an (undiscounted) average patient OA development of 5 years compared to current treatments: $\Delta\text{QALY} = 5 \times (0.51 - 0.37) = 0.7$.

Fig. 2. Comparison of the effectiveness gap ($\Delta QALY$) for the five devices and estimated cost savings (ΔC) due to the change from the current treatment to the use of new device with the inclusion of the WTP threshold of €30,000 per 1 QALY.

The $\max\Delta\text{CostPP}$ estimated based on this ΔQALY , and the estimated ΔC of €1,100 per patient (based on the length of hospital stay, theatre time, and material cost reported in the literature) was: $\max\Delta\text{CostPP} = (\text{€}30,000 \times 0.7) + \text{€}1,100 = \text{€}22,100$. The IHP device is predestined to be used as a regenerative treatment device used as unit per patient, and thus: $\max\Delta\text{CostPP} = \max\Delta\text{CostDU} = \text{€}22,100$.

The majority of the devices align well with the margin production cost (C_{margin}) estimated based on the device development costs (CDD) provided by the manufacturers. The biggest difference between C_{margin} and CDD was found for the RAPAI device, with $\text{C}_{\text{margin}} = \text{€}1,645,120 - (20 \times \text{€}3,528) = \text{€}1,574,560$, and the CDD estimated by the manufacturers equal to €150,000 per device unit. The lowest difference between the C_{margin} and the CDD was estimated for IHP device, based on the assumption that the total cost of the ACI arthroscopic procedure is estimated as €11,980 per patient with the inclusion of the cell culture costs (€4,000). The C_{margin} was thus: $\text{C}_{\text{margin}} = \text{€}22,100 - \text{€}11,980 + \text{€}4,000 = \text{€}14,120$. The estimated by the manufacturers cost of the development of an IHP unit was equal to €8,000, which is within the estimated margin production cost. Figure 3 presents comparison of the estimated production costs per device unit (CDD) and the estimated results of the margin cost (C_{margin}) for five devices.

Fig. 3. Comparison of the estimated production costs per device unit (C_{DD}) and the calculated results of the margin cost (C_{margin}) for five devices.

3.3 ROI

The analysis of ROI revealed that the device with the highest potential commercial value for the company in the first year was RAPAI. The imaging device manufacturers estimated the production price of one device unit as €150,000, and the assumed sales volume in the first year based on the number of hospitals in the Netherlands was equal to 10. Thus, ROI was estimated as: $ROI = (\text{€}1,645,120 - \text{€}150,000) \times 10 = \text{€}14,951,200$. The lowest ROI was estimated for IHP device, based on the assumption that estimated number of patients that will undergo the surgery with the use of new device in the first year is equal to 500. The ROI in the first year was thus estimated as: $ROI = (\text{€}22,100 - \text{€}8,000) \times 500 = \text{€}7,050,000$.

4. DISCUSSION

The combined Headroom and ROI analysis proposed in this study can be used to compare project investments based on the commercial viability of medical devices and support go/no-go investment decisions regarding medical devices in the early stages of the development [27]. The analysis of six devices enabled identification of the device with the highest potential commercial viability (RAPAI), and two devices which had the lowest potential commercial viability (HBM and IHP). This study shows that the estimation of the headroom at the early stages of medical devices development is a useful alternative to other, more complex methods, such as CEA, CBA and CUA methods. Those methods usually take parameter estimates from randomized controlled trials or large observational studies, which facilitates the estimation of real-world effectiveness [12, 16].

There could be two distinct reasons for SMEs to implement the Headroom method. Currently, pricing strategies of devices are based on a cost-plus approach and the Headroom may facilitate a pricing strategy which is based on the relative value-based pricing. Second, implementing Headroom methods, forces SME's to identify the most important parameters that drive the value of the medical device, which can steer their development and clinical research strategy.

The cost-plus pricing is a rather conventional approach, under which the direct material cost, direct labour cost, and overhead costs for a product are added together with a mark-up percentage to create a profit margin, in order to establish the price of the product. This method is not appropriate for setting the price of a medical device to be launched in a highly competitive market, mostly, because it does not factor in the price of potentially similar devices charged by competitors. A shift from cost-plus

pricing into the value-based pricing approach is therefore gaining more attention. The value-based pricing approach is usually difficult to implement, but crucial to conduct at the very early stages of product development [27]. From the earliest stages of device development, the presented method could inform manufacturers about the cost of the medical device under development and its potential value, perceived or estimated, to the customer [28].

The Headroom method could also help manufacturers to identify parameters that drive the future value of the device and analyse the uncertainty surrounding the device's value by performing sensitivity analysis. With sensitivity analysis, the assumptions about the future are made at the early stages of the device development, to stimulate strategic thinking and to support the decision making process [29, 30]. Furthermore, getting more accurate estimates for a few key parameters at the early stages of the development would allow manufacturers to add more parameters to the equation later on, and thus iteratively and efficiently decrease the overall decision uncertainty. In that way, decision uncertainty stemming from the use of early economic data, that is likely to be different from real-world data, can be addressed, and thus one of the biggest recognized challenges of early stage assessment can be partially overcome [31]. It could be a feasible addition to the formal methods to address uncertainty that currently dominate in the early stages of medical device development, such as eliciting the views of experts [32, 33]. Especially as criticism of those methods is increasing, because opinions of experts are usually found to be too optimistic and typically the variance around them is estimated to be too narrow [34, 35].

The major limitation of presented method is the fact that the headroom calculation requires an estimation of QALYs [12, 16]. Most of the time QALYs may be obtained from literature, but the quality of data obtained that way vary and sometimes is simply outdated. While the relative outcomes allow prioritization of devices, the absolute outcomes of the presented combined method are indicative only as the inputs are based on existing studies, and assumptions from experts, manufacturing team or the authors of this paper if no literature was available. Furthermore, the Headroom analysis was estimated under the assumption that the incremental health benefit, as monetized by the WTP for one QALY, together with the potential cost-savings, would be fully recouped by the manufacturer in the sales product price, which may not be the case. Another limitation is that headroom calculation is based on the societal WTP threshold, while there are many formal and informal WTP thresholds used, and the actual decision is not only based on this threshold. Indeed, there are various other criteria that are relevant to health policy decisions. Furthermore, the ROI in the

presented method is calculated based on a one year time horizon, which is arbitrary, considering that ROI is usually based on longer time horizons. However, ROI presented in this paper is aimed to determine if new medical device development is feasible very early in the development cycle. At that point, calculating the ROI as a fraction or percentage rate of return is speculative when the market and thus potential investment are unknown. Later in the device development, when the manufacturers can more precisely estimate an expected profit, ROI must be discounted over a time horizon chosen to reflect the strategy of the company.

Finally, it is important to realize that the financial value of medical device projects in the R&D stages is difficult to assess as they are subject to considerable technological and market/demand uncertainties. Technological uncertainties are mostly inherent to the inability of manufacturers to guarantee safe and effective devices that can pass clinical trial hurdles and gain regulatory approval (e.g. due to unforeseen side effects) [36]. Market uncertainties concern the unpredictability of the future value of a medical device as estimated during R&D, which may be affected by e.g. competitor's devices or incomplete information regarding the reimbursement scheme for a medical device. This also implies that a technical success of the medical device gives no guarantee for commercial revenues.

5. CONCLUSIONS

Headroom analysis combined with the calculation of ROI is a feasible, useful, and informative tool for assessing the potential commercial viability of medical devices under development. It might be an answer to the growing need to performing value-based pricing of medical devices at the early stages of the development, replacing the dominating cost-plus pricing approach. Manufacturers may use the method to decrease uncertainty around the decision making process through the use of best/worst case scenarios. However, the danger of linking "fake money" offered by the thresholds assumptions to the "real money" of a business cases must not be overlooked.

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Chapter 6: Adapting the New Product Development Scoring Tool to Identify Medical Device Success

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ABSTRACT

Background: The development of medical devices is widely recognized as a complex, long and expensive process. It is of utmost importance to predict at the early development stages whether a new device will have a chance to succeed on the healthcare market, to inform the decision-making process of the manufacturers and diminish the high failure rate.

Objective: An adapted new product development (NPD) scoring model is proposed as a potential tool to guide decisions of the medical device manufacturers at different developmental stages.

Methods: An existing, widely applicable NPD scoring model was adapted to accommodate the characteristics of the healthcare market. The potential functionality of the adapted model as a tool to predict market success was illustrated in two medical devices under development.

Results: In the illustration of the model with two devices, it was revealed that one of the devices assessed, a regenerative biomaterial, had 85% chance to be successful on the healthcare market. It should thus get a “Go” decision for further development, as a profitable investment project. The second device, a gait improvement device, had 74% chance to be successful. The manufacturers would be advised to perform additional assessment activities within the “Recycle” or “Hold” decision.

Conclusions: Once validated, the adapted model could help to inform the manufacturers in the early stages of the development which medical devices will have the potential to compete effectively in a specific market segment and to generate profit. This kind of information is needed to support successful portfolio management and project prioritization, and thus could lead to more informed resource allocation decisions within the company.

1. INTRODUCTION

Research and Development (R&D) spending as a percentage of sales in the medical device industry is nearly as high as 12 percent [1, 2]. At the same time the development process is characterized with a very high failure rate at every lifecycle stage [1]. The implementation and launch of a medical device is strongly influenced by various aspects, e.g. added value to patients and society, recommended use in the care pathway, market regulations and compliance with reimbursement schemes. Once the device is marketed, the manufacturers face other challenges, i.e. increasingly shorter device lifecycles (sometimes no longer than 18 months), fast growing competition, and increasing demands by users [1]. In order to survive in that challenging industry, the manufacturers of medical devices are under pressure to identify a clear added value of their devices early in the lifecycle, and to conduct the development process as efficiently as possible [1, 3]. Understanding the commercial viability of medical device implies that the manufacturers anticipate on how their device will meet market, regulatory, and payers demands before the device gets into the development pipe and throughout the development itself [1, 3, 4]. The development of the “unsuccessful” or “commercially not viable” medical devices could thus be stopped before detailed design and development activities are undertaken, and additional resources are invested [5-8].

Scoring models have been proposed as a tool to support the New Product Development (NPD) process, by informing Go/Kill/Hold/Recycle decisions almost 30 years ago. However, they are still used in the industry both for NPD project prioritization and for the portfolio management [9-13]. Used iteratively alongside NPD, scoring models help to avoid several common problems typical to NPD, such as unclear product strategy, inadequate product definition, unresolved technical uncertainties, inadequate assessment of market needs, unclear project objectives, and shortage of key resources [5, 14, 15]. Scoring models based on the list of factors correlated with commercial viability of medical devices could serve as a predictor of whether a new device will reach the market and be reimbursed [5-8]. They could also support the decision-making process of manufacturers alongside the device development, starting from the early lifecycle stages [5-8, 16].

A simple scoring model that could evaluate commercial viability of medical devices during their development is therefore both useful and necessary [16]. Following empirical research on the factors associated with NPD success by Robert Cooper [3, 17-19], the NewProd model was introduced. The NewProd tool predicts the likelihood of “success” or “failure” by gathering and analysing information from

various stakeholders with the use of the questionnaires and translating this input into the managerial actions within the company [3, 10, 19]. The quantitative analysis by stakeholders forms the basis of the NewProd model and is followed by a qualitative discussion, in which the strong and weak points of the project under development are identified, and specific recommendations for further development are provided. This model was designed to decide about new NPD project proposals and to iteratively screen projects under development throughout the whole NPD lifecycle [3, 9, 10, 19].

The NewProd model has been replicated and validated within a number of companies, and also in different settings [17]. It could thus be an adequate tool to evaluate commercial viability of medical devices and stimulate the decision-making process of the manufacturers. In particular SMEs within the medical device industry might benefit from such tool, as it is recognized that they often lack the resources to conduct such assessments [20, 21]. Although perceived as potentially beneficial, some adaptations are required before using in the medical device industry, namely: 1) the model should be more specific to the development of medical device and its unique characteristics [22]; and (2) the analysis should provide a transparent and aggregate outcome that would be easy to understand by the medical device manufacturers.

Therefore, the aim of this research was to illustrate how the NewProd model presented by Cooper can be adapted to serve as a potential medical device development decision guide for the SMEs at different stages of device development. Potential application of that adapted model was presented with two case studies of medical devices, which are currently being developed by the spin-off companies and research groups within the University of Twente (UT) in the Netherlands.

2. METHODS

2.1 The NewProd model

The NewProd model was developed in 1979 by identifying 48 different factors that influence the new product future outcome [3]. Those factors were analysed based on 195 product cases from 103 Canadian companies with the use of the data gathered on a posteriori basis [23]. Each product was analyzed by the project managers involved in the development of those products based on 48 factors using zero to ten scales, and rated for their commercial success chance on a scale from -

5 to +5. Cooper defined the “success” of a NPD as a product that met or exceeded the acceptable financial return for this type of investment [24]. The analysis resulted in the sample of 102 product successes and 93 product failures, together with 48 factors [16, 23, 24]. The 48 factors were further reduced to 13 dimensions, and multiple regression was used to correlate the degree of the commercial success with these 13 dimensions. From these 13, only eight dimensions were included in the final regression model [23]. Three dimensions describe the comparative advantage of the new product, i.e. Product Superiority & Uniqueness (PSU), Economic Advantage of Project (EP), and the Product scope (PSC). Another three dimensions measure the fit between the project and the company characteristics, namely the overall Project-Resource Compatibility (PRC), Newness to the Firm (NF), and Technological Resource Compatibility (TC). The last two dimensions describe the nature and magnitude of the potential market, i.e. Market need, growth and size (MN), and Market Competitiveness (MC).

The eight key dimensions of the NewProd model constitute a base of a questionnaire with 30 statements, which evaluators’ rate by indicating their level of agreement on the scale from zero-to-ten (0=strongly disagree, 10=strongly agree). The evaluators are also asked to indicate how sure or confident they are about each answer to capture the uncertainty around NewProd model results, where ten=100% confident; I am certain about this answer, and zero=no confidence; a pure guess. Evaluators input is used to compare the profile of the project to the profile of past projects whose outcomes are known [17]. In the same time the results of the questionnaire pinpoint the strengths and weaknesses of the new project, and indicate the likelihood of commercial success [17].

The predicted degree of NPD success and failure, called the “Product Score” (PS), is derived from the regression equation with the inclusion of an intercept of 0.328 [16, 23]. The PS scale ranges from -5 to +5. According to Cooper, a project with a PS of -5 to 0 predicts a project “failure”, whereas a PS of 0 to +5 indicates a project “success” [16, 23]. The results of Cooper’s research were validated with the cross split half method. The overall predictive ability of the model, based on the comparison of the predicted and actual outcomes of the projects analysed by Cooper, is equal to 84%, with a mean error of 2.47 [23]. That result was further validated by Bronnenberg and van Engelen [16].

2.2 The adaptation of the model for medical devices industry

To adapt the model to the medical device industry the factors within the dimensions of the NewProd model were compared with four groups of determinants that correlate with successful implementation of innovation in healthcare, as determined by Fleuren et al. [25]. The factors identified as relevant for the success of medical device development process were then grouped in a new dimension, namely the “Healthcare Compatibility Fit” (HF). Further validation of those factors correlation with the specifics of the healthcare market was done with the literature search. Table 1 presents the factors included in the HF dimension, together with the references from the literature search.

Table 1. Factors proposed to be included in the Healthcare Compatibility Fit dimension.

Factors	References
Clear protocols/guidelines for the future use of the device	[25-28]
Necessity of potential users of the device to acquire new skills/knowledge	[25, 29-31]
A good fit between the device and the existing work procedures within the potential application area	[25, 32-36]
No financial burden of the device imposed on patients (insurance coverage)	[25, 37, 38]
The device fit the current reimbursement schemes	[25, 30, 37, 38]
Willingness of the potential users to accept the device	[25, 26, 29, 30, 33, 37-41]
Company skills to collaborate with appropriate healthcare specialists are more than adequate to start the device development	[25, 29, 30, 32-36]
The ease of the device to be subjected to clinical trials	[25, 27, 29]
The device fit with the current infrastructure and resources of the healthcare organization	[25, 28, 29, 32, 33, 35, 40]

Based on the factors identified original questionnaire developed by Cooper was supplemented with additional 17 statements captured within the HF dimension. The final adapted NewProd model questionnaire consisted of the total number of 47 statements distributed over nine dimensions.

For the adapted NewProd model demonstration purposes it was assumed that the weight of the new HF dimension will be equal to the weight of the Overall Project-

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Resource Compatibility dimension, and thus the same Regression Coefficient (RC) was used for both dimensions ($RC=1.13$). However, a thorough validation of that assumption should be conducted, as it influences the validity of the whole product score outcomes.

2.3 Illustration of the adapted NewProd model on two cases

2.3.1 Cases description

The potential functionality of the adapted NewProd model was illustrated on two case studies of disruptive medical devices, which are currently being developed by the spin-off companies and research groups within the UT. This research is not allowed to share the details over the medical devices used as a case studies, however, a generic description of an underlying idea behind the technology is presented in Boxes 1 and 2.

Box 1. Novel regenerative biomaterial.

A regenerative biomaterial is being developed to be applied for the organs on veins reconstruction during the surgeries. The aim of that innovation is to help the patients undergoing specific surgeries to get better treatment, recover faster and improve their clinical outcomes. The development of the novel regenerative biomaterial is currently in the Preclinical research of the Prototype development stage.

Box 2. A device to improve the gait of patients suffering with neurological disorders.

Some neurological disorders patients suffer gait disturbances and greater chances of falling, due to the neurodegeneration in the brain. A gait improvement device can provide sensory cueing to patients during daily living activities. That innovation could dramatically improve the quality of life of neurological patients, increasing their independence and confidence. The development of the gait improvement device is currently in the Phase I trials of the Prototype development stage.

2.3.2 Selection of the project teams

Two project teams were asked to evaluate the medical device cases by filling-in the questionnaire of the adapted NewProd model. The evaluators were selected using specific criteria: (1) evaluators were members of the project team or their core

expertise fitted the topic of the project, and (2) the evaluators team was as multidisciplinary as possible, with the focus on the evaluators with both the medical and technical expertise. For the novel regenerative biomaterial, the team consisted of four evaluators (n=4). Two evaluators were affiliated with an academic research group: a Technical Physician/PhD Candidate and a Junior Researcher. Two other evaluators were employed by the biomedical company collaborating with the research group on the regenerative biomaterial development. The evaluators group from the gait improvement device project team consisted of two people (n=2): Doctor of Medicine/PhD Candidate and a Junior Researcher with a technical background. After selection, a preliminary meeting was organized to explain the purpose of the research, and the features of the adapted model to all evaluators. During the meeting the definitions used in the model were also explained. The preliminary meeting lasted for around 20 minutes.

2.3.3 Questionnaire

After the preliminary meeting each project evaluator received an electronic questionnaire via e-mail. The questionnaire described the aim of the adapted model and the steps involved. The evaluators were advised to fill-in the questionnaire individually. All variables were measured on the zero-to-ten Likert scale, as self-reported attitudes toward a range of statements. The scales were anchored at the extremes and went from “strongly disagree” (0) to “strongly agree” (10). The anchor phrases were provided to help define what is meant by ten or zero. The respondents were encouraged to give their best estimate to every answer. For each question corresponding to particular success factor the respondents were also asked about the confidence level of each answer they gave on the scale from zero to ten, where ten = 100% confident, and zero = no confidence at all. The data from the questionnaires was analysed using a Microsoft Excel spreadsheet.

2.3.4 Data analysis and reporting

The data analysis started with the calculation of the uncertainty in values within the group of evaluators. It was based on the maximal and minimal possible values (MaxV, MinV) of each individual variable (V) filled-in by the evaluators included the corresponding confidence level (CL) that evaluators estimated for every statement variable (equations 1 and 2). The minimum value addresses the lowest minimum value in the group of evaluators as scored on a factor. The maximum value addresses the highest maximum score that one of the evaluators gave on a factor.

$$\text{MaxV} = \text{MIN}(10; V + (0,5 * (10 - CL))) \quad (\text{eq.1})$$

$$\text{MinV} = \text{MAX}(0; V - (0,5 * (10 - CL))) \quad (\text{eq.2})$$

Next step of the calculation was focused on a group value in the form of a median of all evaluators' minimum values, values scored, and maximum values on the factor, where n equals the number of variables (equation 3 and 4).

$$\text{For the group with odd variables:} \quad \text{Median} = ((n + 1)/2) \quad (\text{eq.3})$$

$$\text{For the group with even variables:} \quad \text{Median} = [((n)/2) + ((n)/2 + 1)]/2 \quad (\text{eq.4})$$

The calculation of the medians was followed with an estimation of the average of those medians for each particular dimension, substituted as a Factor Score (FS) in the PS calculation (equation 5).

$$\text{FS} = 1/n \times (\text{Median1} + \dots + \text{Mediann}) \quad (\text{eq.5})$$

The adapted PS equation, i.e. complemented with the newly defined HF dimension, was calculated with the use of normalized regression coefficients, in which all weights are summing up to one. Based on the weights determined and validated by Cooper [23], and under the assumption that the weight of new dimensions is equal to the weight of the Overall Project-Resource Compatibility dimension. The PS in this research was calculated as (equation 6):

$$\begin{aligned} \text{PS} = & 0.496\text{DSQ} + 0.323\text{CPF} + 0.323\text{HF} + 0.228\text{MP} + (-0.218)\text{EP} \\ & + (-0.100)\text{NC} + 0.097\text{TC} + (-0.085)\text{MC} + (-0.064)\text{DS} \end{aligned} \quad (\text{eq.6})$$

Final calculation step was to express the PS results in percentages, where PS=10 corresponds to 100%. The aim of that step was to apply certain thresholds to the PS results, and with the help of those thresholds to easier guide decisions-making processes of the manufacturers. Following thresholds to the results of the PS calculation were proposed:

(1) a PS equal or higher than 75% indicates a project “success”, and based on that score the manufacturers will be recommended to make a “Go” decision, where the action plan for the next device development stage is approved, including timeline, resources, budget, deliverables and date for the next gate meeting;

(2) a PS below 75%, but above 35% indicates that a manufacturer should make either the “Recycle” decision, where the device development is returned to the previous stage for further work within the new application area, as specified by the gatekeepers, or a “Hold” decision, where the device development is put on hold list for review at a future date;

(3) a PS equal or lower than 35% indicates a project “failure”, and in that case the manufacturers are suggested to make a “Kill” decision, where the device development is archived, no work is done, and no further resources are committed. In addition to the calculation of the PS, a graphical representation of the questionnaire results for every dimension of the model was prepared.

3. RESULTS

3.1 Product scores calculation

The results of the calculations that led to the estimation of the PS are presented in table 2. Figure 1 presents the overview of the group scores on success factors within the dimensions for regenerative biomaterials (a) and for the gait improvement device (b).

Table 2. The input to calculate Product score (PS) with the adapted NewProd model.

Dimension	RC ³	Regenerative biomaterial				Gait improvement device			
		MaxVD ¹	MinVD ²	CL	FS	MaxVD ¹	MinVD ²	CL	FS
Device Superiority & Quality (DSQ)	0.496	9,7	4,8	7,5	7,6	9,0	5,3	8,0	6,9
Company Project Fit (CPF)	0.323	10,0	3,4	6,3	7,6	9,5	4,4	5,7	7,6
Healthcare Compatibility Fit (HF)	0.323	9,9	4,1	6,9	9,0	9,3	2,8	5,3	6,7
Marketplace (MP)	0.228	10,0	5,1	8,0	8,3	8,3	2,6	7,3	5,3
Economic Advantage of Device (EP)	- 0.218	9,0	4,0	7,4	6,8	7,5	2,0	7,3	6,9
Newness to the Company (NC)	- 0.100	10,0	1,6	6,3	7,6	8,3	2,0	6,1	4,6
Technological Compatibility (TC)	0.097	10,0	3,8	6,7	7,8	9,8	4,0	5,9	7,1
Market Competitiveness (MC)	-0.085	8,8	1,5	7,3	6,0	9,4	2,7	8,2	6,2
Device Scope (DS)	- 0.064	10,0	5,5	8,1	8,8	8,3	3,8	7,3	6,5
Results		PS=8.46=85%				PS=7.38=74%			
		Total score FS (average) = 7,7				Total score FS (average) = 6,4			
		Total score MinVD (average) = 3,8				Total score MinVD (average) = 3,3			
		Total score MaxVD (average) = 9,7				Total score MaxVD (average) = 8,8			

¹MaxVD – average of the maximal possible value of each individual variable within the dimensions

²MinVD - average of the minimal possible value of each individual variable within the dimensions

³RC – Regression Coefficients recalculated as the normalized regression coefficients

Figure 1a. Group scores on success factors within the dimensions: regenerative biomaterials

min, median, max

Figure 1b. Group scores on success factors within the dimensions: Gait improvement device

min, median, max

The calculation of the PS for the regenerative biomaterial project was equal to 85%, and for the gait improvement device project it was equal to 74%. The manufacturers of the regenerative biomaterials would thus be recommended to make a “Go” decision, where the action plan for the next device development stage is approved, including timeline, resources, budget, deliverables and date for the next gate meeting. Conversely, the gait improvement device manufacturers would be recommended to make the “Recycle” decision, where the device development is returned to the previous stage for further work within the new application area, as specified by the gatekeepers, or a “Hold” decision, where the device development is put on hold list for review at a future date. For the gait improvement device a detailed analysis of all the dimensions was performed, in order to determine what the strengths and the weaknesses of the project are.

3.2 The analysis of project strengths and weaknesses based on dimensions exploration

The analysis of the dimensions based on their corresponding FS showed that the gait improvement device project scored highest on the dimensions: Company Project Fit (FS=7.6), and Technological Compatibility (FS=7.1). This might indicate that the gait improvement device project has a strong technological background, and a good fit with internal resources of the manufacturers. The project scored relatively low on the dimensions Newness to the Company (FS=4.6), and the Marketplace (FS=5.3). This, on the other hand, indicate that the gait improvement device project is not comparable to any other projects that the manufacturers developed so far, and that also explains why the marketplace for that project is completely new for them. Two out of three dimensions with the highest impact on final PS (with the highest RC) also scored quite low: the Device Superiority & Quality (FS=6.9), and the Healthcare Compatibility Fit (FS=6.7). A clear risk factor for the manufacturing company is the limited amount of experience with the kind of technology that is being developed. That strongly relates to the lack of knowledge and understanding of the healthcare market. The manufacturers also do not possess much knowledge on potential competitors and their offerings, which makes it very hard for them to clearly realize what the differentiators of their product are compared to other competitors. Figure 2 presents the detailed overview of the scores on the most risky dimensions for the gait improvement device project: (a) Newness to the Company; (b) Marketplace, (c) Device Superiority & Quality, and (d) Healthcare Compatibility Fit.

Figures 2a-d. The detailed overview of the scoring of two evaluators on four dimensions for the gait improvement device (blue and red triangles represent the values given by the project evaluators with corresponding confidence level, and the green square represents the group value and its corresponding confidence level).

(a) Newness to the Company

(b) Marketplace

(c) Device Superiority & Quality

(d) Healthcare Compatibility Fit

The factors within the Newness to the Company dimension represent the risk of a low level of familiarity of the manufacturers with the specific type of device they are developing. That reflects strongly on their knowledge about the potential competitors, sales channels, users, and buyers. The analysis of the Marketplace dimension shows that the project team see the potential of their device on the market, with regard to the clinical need, and the potential target population. However, limited knowledge on the fast growing and constantly changing healthcare market could be an important drawback to successful implementation. At the same time the Device Superiority & Quality dimension, which reflects the potential differentiators of the device under development with comparison to the competitors on the market scored relatively low as well, reflecting lack of interest in the potential market and clear focus of the project team on the technological part of the development. This finding was further confirmed with the analysis of the Healthcare Compatibility Fit dimension.

Based on the analysis of the four weakest dimensions the gait improvement device project manufacturers were recommended to focus their research activities on gaining more insight in the healthcare market within the selected potential application area. The manufacturers were thus suggested to perform a SWOT (Strengths, Weaknesses, Opportunities and Threats) analysis, which involves specifying a clear objective of the project and identifying the internal and external factors that are favorable and unfavorable to achieve that objective. It thus have an ability to bring quite a broad understanding of the device future market and can help manufacturers to pinpoint the key selling points of their product in the future.

4. DISCUSSION

The aim of this research was to present how the NewProd scoring model can be adapted to be able to specifically support medical device development by adding a ninth dimension, the Healthcare Compatibility Fit (HF). This dimension was build based on the factors identified as correlated with successful implementation of innovation in healthcare. In the adapted model it was decided that the weight of the HF dimension will correspond to the weight of another selected dimension, but it must be acknowledged that those weights have to be developed further.

The potential usability of the adapted model was illustrated based on an example of two case studies: two disruptive medical devices in an early stages of the development. The model estimated that the PS of regenerative biomaterial device

was equal to 85%, and for the gait improvement device project it was equal to 74%. Following the thresholds illustrated in this research the manufacturers of the regenerative biomaterial device should be recommended to make a “Go” decision for further development, as it seems to be a profitable investment project. In the same time the gait improvement device project manufacturers should be recommended to make a “Recycle” or “Hold” decision. Following the results, the analysis of the strengths and weaknesses of the gait improvement device project based on dimensions exploration was performed and specific recommendations for further assessment were given.

One of the strongest advantages of the scoring models, such as the adapted NewProd model that use the input from various stakeholders is that it requires iterative communication between project team members and external stakeholders. That leads to greater organizational integration, i.e. the degree of cooperation and communication between internal and external stakeholders, which is proven to influence directly the market success of new products [42, 43].

In the same time a limitation of the scoring models relates to the general nature of all the models based on checklists and factors scoring. Those models rely heavily on the subjective ratings of the project evaluators, and might be judged as not very accurate. However, at the early stages of the medical devices development, which are crucial for the medical device successful development and implementation, subjective opinions are usually the only data on medical device available. To partially overcome that limitation and to gain more reliable value for each factor it is proposed that the adapted model combines the ratings of the evaluators with the confidence scores.

The major limitation of this study was the assumption made in the incorporation of the HF dimension, i.e. assigning the weight of another dimension without validation. In the same time the potential usability of the model was illustrated on a very small sample of medical devices (two case studies) and on a small sample of the project evaluators (two evaluators for one project and four evaluators for the second project). However, the aim of the presented study was to show how a scoring model could be adopted by the medical device industry, and indicate the need for such a tool to improve the medical device development and implementation process. In order to make that model a tool that could actually be used in practice by the manufacturers, the model have to be validated on a large sample of various medical devices. The predictive value of the model, as a success/failure indication tool, should also be

evaluated with the use of an empirical (a posteriori based) study with known commercial outcomes of selected medical devices.

Final limitation of the adapted model comes from its potentially oversimplified nature, as the model aims to reduce complicated manufacturers decision making process at the gates to an outcome of a simple equation. Recently the majority of the large medical device companies are becoming service providers instead of technology manufacturers, i.e. they deviated from pushing a single devices to adding value to a value chain by developing full solutions instead. In that sense, an adapted scoring model presented in this research might be too simplified to be applied for those companies. However, for the medical device SMEs a simple process to review iteratively at the development gates could be highly beneficial.

It is widely recognized that the gates in the development process of any products are one of the weakest points of NPD, with only 33% of companies having tough rigorous gates implemented within their development process [44]. Although it is not documented how robust the process is exactly in the medical device industry, the authors of this research expect this number to be much lower. The adapted model aims to aid the decision making process of the manufacturers regarding the development of potentially “successful” medical devices, and thus to make the decision gates between various stages more robust, i.e. where the poor projects are spotted early and killed, and projects in trouble are detected and send back for rework or are terminated [45].

5. CONCLUSIONS

The model presented in this research illustrates how the manufacturers of medical devices could be informed from very early stages of the device development if their technology will have the potential to compete effectively in a specific market segment and generate profit. That kind of information could support successful portfolio management and project prioritization, and thus lead to more informed resource allocation decisions within the company. It also facilitates greatly the communication between the manufacturers and external stakeholders. An implementation of the healthcare component into generic NewProd development model have shown to be very useful. Further work is necessary regarding the use of the adapted model as a decision support in the early stages of medical device development.

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Chapter 7: General Discussion

1. MAIN FINDINGS

1.1 Current practices of early assessments of medical devices in the literature and in practice

While early assessments of medical devices have been recommended before, there still is confusion on what it is and how early assessments are performed. Therefore, this PhD thesis started with a thorough systematic literature review, to get a better understanding of the current state of the art in the early assessment and to identify methods to perform those assessments (chapter 2). The results showed that most studies reported in the literature aim at informing manufacturers of medical devices about the potential of their medical device, i.e. to estimate the clinical or commercial potential. This conclusion was further supported using the structured interviews with representatives of the Dutch medical device industry (chapter 3). In addition, the results of those interviews showed that the least developed areas of early assessment are a formal stakeholder's analysis and a health economic evaluation from the perspective of society. This finding is confirmed by the common observation in the literature that medical device manufacturers mostly focus on demonstrating the proof of concept of their medical devices. This narrow view suggests that other components of device value, which significantly influence future implementation and adoption of medical device, are often overlooked [1]. At the same time, according to the scientific literature and expert opinions of the medical device industry representatives, it is clearly recognized that it is crucial for the medical device under development to be evaluated with its potential clinical use in mind, with good understanding of the current healthcare market and with respect to the device potential for bringing benefit to the company and society [2].

Although there is a consensus about the benefits of an iterative use of early assessment methods, the actual development stage at which the assessment should start is less clear. The literature either does not specify the stage of the device development or report that the early assessment was carried out in the prototype product development phase. In contrast, the interviews with the Dutch medical device industry representatives yield that the analysis of the potential market, stakeholders involved and the financial and health economic impact assessment already starts at the idea generation stage. They also indicated that most of the assessment activities are prolonged until the post-marketing surveillance stage. It was, however, very difficult to exactly identify what the interviewees mean with the early assessment activities.

The interviews also conclude that in the medical device industry, of which around 75% is a Small and Medium Sized Enterprises (SMEs), about half of the selected interviewees reported a medium level knowledge of health technology assessment procedures, while one fourth of them indicated low to basic knowledge. Because only 51% of the participants reported that external consultants are hired to perform early assessment activities, it can be concluded that SMEs often do not have enough resources to carry out early assessments at various points in the medical device lifecycle. Proving safety, efficacy and regulatory compliance needed to secure the device reimbursement is thus often too challenging and costly for manufacturers within the medical device SMEs [3, 4]. In the same time, for those methods which were actually reported (in the literature and during the interviews) as being used for the assessment of the device under development there is lack of any evidence on how effective those methods are and what is their actual influence on decision-making process within the manufacturing companies.

1.2 Outline and standardization of early assessments

An interesting finding from the literature review was the absence of a clear theoretical framework for an early assessment. Instead, several, sometimes overlapping frameworks, are described to explain the various components [5-7]. Most of the early assessment theories include a strategic analysis (together with stakeholders analysis) of the medical context, an evaluation of the health economic impact and the early assessment of clinical effectiveness of the medical devices under development. The difficulty with developing a generalized theoretical framework for early assessment is in the dynamics of the device development which requires flexibility, i.e. devices are changing rapidly during their life cycle due to incremental product improvement. The interviews revealed, however, that the majority of the SMEs within the medical device industry focus mainly on the development of disruptive technologies, for which it is even more difficult to find the way to make a proper assessment and create truly commercially viable products.

1.2.1 Early Assessments to Support Strategic Choices in Device Development

The results of the systematic literature review revealed that a large focus of early assessment is on the product related strategic considerations, i.e. those assessments that analyse the potential value of a new medical device compared to best standard or care. Exploration of the potential of a medical device is often used in business plans, to identify the main barriers for successful development in all

stages of development. Two groups of methods are usually employed for such analysis, i.e. literature review and stakeholder involvement methods.

Literature review (both scientific and non-scientific) is usually performed to analyse the market gaps which could be filled-in with the new medical device under development and to search for potential application areas for medical devices. That research can also be combined with more specific and organized SWOT analysis (Strengths, Weaknesses, Opportunities, and Threats analysis), and/or PEST analysis (Political, Economic, Social, and Technological analysis). SWOT and PEST analysis are strongly related to the evaluation of the strategic position of the company itself, but also an evaluation of the potential positioning of the new technology under development on the existing markets. Finally, literature review is also used within the medical device industry to perform horizon scanning, which aims to increase the understanding of what is happening within the medical device industry through identification of new and emerging health technologies likely to have a significant impact on healthcare and also to identify potential competitors of medical device early in the development.

In addition to literature reviews and other inquiries, a formal stakeholder analysis provides a rigorous and transparent view of multiple stakeholder groups regarding the potential device value. Main methods used for stakeholder involvement are qualitative in nature, e.g. focus groups, interviews, expert panels, workshops, or surveys. For the medical device manufacturers, it is very important to start an early dialogue with various stakeholders to understand the evidentiary requirements of various decision-makers involved in the implementation process. That could also help to better align perspectives on the potential value that the medical device could introduce to the healthcare system [8]. However, the interviews with Dutch medical device industry representatives showed that, although they are operating in high technology multi-stakeholder environments, they often fail to recognize the importance of the stakeholders analysis and they face the challenge of finding the right people to collaborate with [9]. Although there are multiple purposes for engaging stakeholders, for the present thesis it was decided to use stakeholder engagement methods to establish the clinical need (and thus potential value) for the medical device under development (chapter 4). One specific methodology that incorporates stakeholder views to support future implementation presented in chapter 4 is scenarios building - a creative method for trend extrapolation and envision of alternative paths into the future. Although never explicitly mentioned during the interviews with the industry representatives, and thus not very common to

be used in practice, this method proved to be very useful in combination with the stakeholder engagement method.

1.2.2 Approaches to Analyse Clinical Benefit of Devices in Development

The results of the systematic literature review revealed that the methods used to analyse clinical benefits of medical devices under development are, in addition to clinical trials, those performed in a controlled laboratory setting such as bench studies, where the performance of the medical device is compared to a gold standard, or clinical practice. The findings of the review showed also that clinical effectiveness assessment of the medical devices starts late, at the prototype product development phase. However, in practice clinical research is also a part of methods assigned to other aims, such as an early economic modelling with the use of a cost-effectiveness analysis (CEA), or cost-benefit analysis (CBA). The clinical evaluation might thus not be mentioned explicitly, but in practice it is probably often performed earlier than at the prototype product development phase.

The interviews within the Dutch medical device industry revealed that the main focus among all the assessment activities that manufacturers perform is on the evaluation of the clinical context of the medical devices, i.e. the environment in which the medical device will be implemented and/or used, related procedures and the clinical outcomes. That is mostly done informally through the interviews and stakeholder meetings, i.e. the conversations with the clinicians/patients, and attending clinical conferences and trade shows. No formal quantitative methods presenting the opportunities for new products and the needs of patients are performed, while these could contribute to the validity and quality of the information that is collected.

In chapter 4 of this thesis it was proposed to combine the qualitative and the quantitative approach to assess the clinical need of a selected medical device under development with the use of a thorough stakeholder analysis. The study implemented a structured approach to stakeholder engagement, including an exploratory phase, a validation phase and an in-depth and systematic review of the epidemiological and clinical literature. The results of this research showed that a mixed methods approach can be a useful instrument for the manufacturers to identify new clinical markets and implementation barriers for new medical devices, even in the early stages of development. The analysis also created awareness of a range of implementation issues that could potentially impact the design, the functionality and actual use of the device. However, despite clear benefits of engaging stakeholders to inform the clinical considerations part of an early assessment of medical devices,

the impact of its outcomes on actual decision making process within the manufacturing company showed only limited ability to change the manufacturers' concept and objectives in medical device development. Other forces, i.e. existing and/or potential funding, and the size of the target population appear to be important drivers as well. Among the explanations why the impact of the research outcomes on the decision making process within the company was so low three are of significant importance: (1) the size of the company and the product portfolio were too small, as it is assumed that small-sized companies carrying single products or Intellectual Property are more strongly pushing the technology itself; (2) the initiative to perform certain types of analysis did not come from the manufacturers or informal investors demanding such input; and (3) the company representatives responsible for ordering or conducting the research did not have sufficient decision power in order to disseminate the research results and to make sure the actions are being taken within the company that follow research recommendations. The question on how the effectiveness of other than early evidence informing clinical considerations could possibly be measured is open for further research.

1.2.3 Early Stage Health Economic Evaluation

The systematic literature review revealed that an early assessment of the health economic impact of medical devices is frequently performed and mainly based on a CEA modelling approach with subsequent probabilistic sensitivity analysis (PSA). The focus of the scientific literature on demonstrating economic impact from a societal perspective 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.

The interviews within the Dutch medical device industry showed that the societal perspective of the economic evaluations, i.e. the question whether society is willing to allocate scarce resources to implement and/or reimburse the new medical device, which is so well represented in the literature, is at best only marginally performed or understood from the company perspective. The financial and business case evaluations, on the other hand, are well developed with return on investment as a main driver for price setting. Although such analyses are essential for business planning and for attracting venture capital, they do not reflect the perspective of the society in which the medical devices will operate. This is very disappointing, as the business case build up by the device manufacturers might become unreliable if the societal benefits are not considered.

The major drawback of the economic evaluation of the medical devices lies in the fact that the financial value of medical device projects in the R&D stages is difficult to assess as they are subject to considerable technological and market/demand uncertainties. Technological uncertainties are mostly inherent to the inability of manufacturers to guarantee safe and effective devices that can pass clinical trial hurdles and gain regulatory approval (e.g. due to unforeseen side effects) [10]. Market uncertainties concern the unpredictability of the future value of a medical device as estimated during R&D, which may be affected by e.g. competitor's devices or incomplete information regarding the reimbursement scheme for a medical device. This also implies that a technical success of the medical device gives no guarantee for commercial revenues. Those uncertainties also make it challenging for the manufacturers to provide strong economic evidence of the potential value of their medical device under development. It also makes it very difficult, or even impossible for most of them, to find investors willing to support their projects. As the healthcare resources are getting more and more stringent, the ability of a company to prove to potential investors that their technology will be cost-effective became a compelling argument supporting its future development [5].

The Headroom Method is a specific method that is proposed in the literature to estimate the maximum reimbursable price, advocated as a very useful technique for the early health economic assessments of medical devices because of its simplicity [5, 11-13]. The application of the Headroom Method combined with the Return on Investment (ROI) calculation to estimate potential commercial viability of several medical devices under development was presented in chapter 5 of this thesis. The combined Headroom and ROI analysis can be used to compare project investments based on the commercial viability of medical devices and support go/no-go investment decisions regarding medical devices in the early stages of the development [27]. This study showed that the estimation of the headroom at the early stages of medical devices development is a useful alternative to other, more complex methods, such as CEA and CBA methods. Those methods usually take parameter estimates from randomized controlled trials or large observational studies, which facilitates the estimation of real-world effectiveness [5, 13]. There are two distinct reasons for the medical device manufacturers to implement the Headroom method into their evaluation practices: (1) the Headroom may facilitate a pricing strategy which is based on the relative value-based pricing instead of the currently dominating cost-plus approach, and (2) it might force SMEs to identify the most important parameters that drive the value of the medical device, which can steer their development and clinical research strategy. The major limitation of the Headroom method is the fact that the headroom calculation is conducted based on

the elicitation of health utilities used to estimate Quality-Adjusted Life Years (QALYs) [5, 13]. To make reliable calculation of the headroom manufacturers should be able to make a common-sense estimate of a utility value for a given health state based on information available, i.e. from the scientific literature. In practice, however, that is often very difficult for the manufacturers to estimate. One of the proposed ways to replace QALYs is to conduct discrete choice experiments (DCEs) to explore individuals' valuations of the various attributes of treatments [14]. However, further research is needed to test the DCE approach in the real decision-making situations. Another limitation of using Headroom method is that it is based on the societal Willingness-to-Pay (WTP) threshold, where there is no clear consensus in the literature about what is considered a reasonable amount to pay for a one QALY gained [15]. It is also quite dangerous to link the "fake money" suggested by the WTP thresholds assumptions to the "real money" of a business cases.

1.2.4 Decision Support in Medical Device Development

Previous sections of this discussion mainly focused on early assessment activities as reported in the scientific literature and in practice by the interviews respondents, stakeholder engagement value in clinical need estimation and early stage health economic models to evaluate the commercial viability of medical device. The main challenge, however, is how to help medical device manufacturers to use the information gathered with different methods used for early assessment of medical devices in business planning and R&D decisions. Chapter 6 of this thesis therefore presented slightly adapted to fit the healthcare industry scoring model, which is widely distributed within the various industries for NPD, namely the NewProd model. The objective was to show how a scoring model incorporating perspectives from multiple NPD project team members could be adopted by the medical device industry.

The idea behind the model is simple: it contains questions related to all the important strategic considerations, both product and company related, clinical considerations, and economic evaluations that the manufacturers must take into account during various stages of the medical device development. Based on the input from several project team members the model estimates the potential commercial viability of the medical device under development. If the commercial viability is low, specific assessment activities are proposed to the manufacturers to make sure that further medical device development will be most likely to succeed, or it should be stopped. The model is based on an iterative approach, which is essential for the model to give as reliable estimate as possible, as it forces manufacturers to move from simple

analyses early in the device development to more sophisticated methods to gather evidence in the later stages. In that way all the new evidence (e.g. clinical and economic data) gathered as the device development progresses is implemented in the model, and the indication whether or not the device under development could become a commercially viable product is updated at various development stages. In the same time some of the model input relies strongly on the dialogue with the external stakeholders, forcing manufacturers to leave the medical device development side and engage in the dialogue with various parties (e.g. clinical experts, patients, reimbursement companies' representatives). Ideally, the outcome of the model should be used within the manufacturing companies to improve the assessment practices during the development of novel medical technologies and to gear the innovations towards their expected performance.

One of the strongest advantages of the scoring models that use the input from various stakeholders, such as the adapted NewProd model presented, is that it requires iterative communication between project team members and external stakeholders. In the same time a limitation of the scoring models relates to the general nature of all the models based on checklists and factors scoring. Those models rely heavily on the subjective ratings of the project evaluators, and might be judged as not very accurate. However, at the early stages of the medical devices development, which are crucial for the medical device successful development and implementation, subjective opinions are usually the only data on medical device available. To partially overcome that limitation and to gain more reliable value for each factor it is proposed that the adapted model combines the ratings of the evaluators with the confidence scores. Final limitation of the adapted model comes from its potentially oversimplified nature, as the model aims to reduce complicated manufacturers decision making process at the gates to an outcome of a simple equation. However, for the medical device SMEs a simple process to review iteratively at the development gates could be highly beneficial.

2. RECOMMENDATIONS

With the increasing regulatory demands for medical device manufacturers and the need for efficient allocation of resources, a thorough understanding of the mechanisms to build the evidence at early stages of medical device development is required. The inclusion of iterative early assessment methods must thus become an integral part of the medical device development process. This process already started, however the iterative use of medical device assessment alongside their

development is relatively new and unknown. Many questions remain, e.g. on the use of the most appropriate methods, on the level of an actual understanding of the methods outcomes by the device manufacturers, or the real influence of those outcomes on the decision making process within the medical device companies. For an early assessment to become a practical tool to support manufacturers in medical device development, some basic classification and harmonization of methods are necessary. That could also lead to the development of a structured guidance of best practices that manufacturers could follow, which would greatly benefit the industry as a whole.

Future studies should also aim to link early indicators of medical device success gathered through early assessment activities within the manufacturing company to the actual implementation of the medical device. That way the manufacturers could better understand what the added value of an early assessment activities is and they would be less hesitant to use their time and money to perform an assessment, knowing that those activities will increase the chance of their device successful development and implementation.

However, the focus of an early assessment should not only be on the use of various methods to inform different assessment parts, e.g. economic evaluation. It is also crucial for the manufacturers to get some guidance for their decision making processes regarding the device development in a form of a checklist they could follow once the development progresses. The adapted NewProd scoring model presented in this thesis aims to become this kind of a decision support tool starting from the early stages of the medical device development. Its purpose is not only to guide the manufacturers through the most important questions they should be able to answer with regard to their medical device under development, e.g. who will be the future user of your device? It also aims to build an awareness within the manufacturers of all the knowledge they should be building while the device development progresses, and of the importance of the dialogue with various stakeholders, which should start early in the device lifecycle. However, further work is necessary in order to make the adapted NewProd model a tool that could actually be used in practice. First of all the model have to be validated on a large sample of various medical devices. And after that the predictive value of the model, as a success/failure indication tool, should be evaluated with the use of an empirical (a posteriori based) study with known commercial outcomes of selected medical devices. Only then the real value of the model can truly benefit the medical device industry.

3. CONCLUSIONS

Early assessment holds the promise for more informed decisions that could improve the pace and the efficiency of the device development and guarantee their successful implementation in the future. However, there is no well-developed framework for early assessment, which makes evaluation of its value difficult. Although many methods seem to be in use within the medical device industry, there is no clear understanding of how those methods are conducted, what evidential requirements are to be met and how this supports the decision-making process in companies.

Stakeholder engagement is an important first step to identify unmet clinical needs, as well as clinical, organizational and regulatory barriers relevant for strategic decision making. It should thus become an integral part of the device development process. However, the results of the stakeholder engagement research conducted within the framework of this thesis indicate that the stakeholder engagement alone has only limited ability to change the manufacturers concept and objectives in medical device development. Future studies should aim to link early indicators of medical device success, as perceived by clinical stakeholders, to its actual implementation.

Early health economic modeling is promoted as an important part of an early assessment of medical devices. While there is a focus on the use of complex methods, such as CEA or CBA, the Headroom method seem to have the most flexibility to link the potential ROI for the manufacturers with the value added to the healthcare system. It might thus be an answer to the growing need of performing value-based pricing of medical devices at the early stages of the development and define their potential commercial viability.

The NewProd model could become a practical tool to support manufacturers in medical device development, offering a decision support about the potential of medical devices to compete effectively in the market and generate profit. It could thus support successful portfolio management and project prioritization, and lead to more informed resource allocation decisions within the company. However, further work is necessary regarding the actual use of the adapted model as a decision support in the early stages of medical device development.

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Summary

This thesis was written under the assumption that the implementation and adoption of new medical devices can be supported by an early assessment of economic and clinical perspectives. The early stages of the medical device development are found crucial, as early in the lifecycle the device development process can either emerge or conclude without major financial drawbacks for the company. An assessment of medical devices starting at the early stages could result in a decrease of the failure rate at each stage of further medical device development, and thus in an increased Research and Development (R&D) efficiency. This, on the other hand, could lead to more successful reimbursement of new medical innovations and better prioritization of devices that are most likely to succeed.

However, as the iterative use of medical device assessment alongside their development is relatively new and unknown, many questions remain. To answer some of those questions, this thesis particularly addressed the:

1. clinical need and methods to engage various stakeholders within the medical device development,
2. the evaluation of the commercial viability of medical devices early in the lifecycle to prioritize development of the most “beneficial” technologies using potential added value to society and, hence, economic returns,
3. the adaptation of a decision support tool for the manufacturers to be used alongside the medical device development process.

First of all the focus of the research was on investigating the current state of the art in the early assessment and the identification of an assessment methods reported in the literature that help to inform decisions during the development stages of medical devices (Chapter 2). The results obtained from a literature study were synthesized in a form of a survey for the Dutch medical device manufacturers that aimed to investigate the use of early assessment methods in practice (Chapter 3).

The results of these studies indicated that an early assessment holds the promise for more informed decisions that could improve the pace and the efficiency of the device development and guarantee their successful implementation in the future. However, there is no well-developed framework for an early assessment, which makes evaluation of its value difficult. Although many methods seem to be in use within the medical device industry, there is no clear understanding of how those methods are conducted, what evidential requirements are to be met and how this supports the decision-making process in companies.

Furthermore, the understanding of how an early assessment in the medical device industry is conducted determined the choice of the methods/approaches, identified as promising and relatively easy to use, to be tested on the examples of real medical devices under development in further research. Medical devices that were used as case studies during this research period were all being developed by a spin-off companies and research groups of the University of Twente. They were selected as a convenience sample based on their characteristics to cover the whole range of disruptive and incremental innovations of both add-on supplies as well as therapeutic and diagnostic devices.

As a part of the Clinical consideration, the focus was first on applying iteratively a stakeholders analysis as a tool to identify potential clinical need for new medical device (Chapter 4). The literature study on stakeholder engagement indicate that it can be an important first step to identify unmet clinical needs, as well as clinical, organizational and regulatory barriers relevant for strategic decision making. It should thus become an integral part of the device development process. However, the results of the stakeholder engagement research conducted within the framework of this thesis indicate that the stakeholder engagement alone has only limited ability to change the manufacturers concept and objectives in medical device development.

Stakeholder engagement research was followed by simple health economic calculations based on the Headroom method combined with the Return on Investment analysis (ROI) to determine the potential commercial viability of several medical devices (Chapter 5). Early health economic modelling is promoted as an important part of an early assessment of medical devices. While there is a focus on the use of complex methods, such as cost-effectiveness analysis or cost-benefit analysis, the Headroom method seem to be best aligned with the requirements in early development. Also, the headroom methods seem most suited to link the potential return of investment for the manufacturers with the value added to the healthcare system. It might thus be an answer to the growing need of performing value-based pricing of medical devices at the early stages of the development and define their potential commercial viability.

Finally, in Chapter 6 a general scoring model widely used to evaluate New Product Development (NPD) was adapted to fit into the medical device industry. The results of that research indicated that NewProd model could become a practical tool to support manufacturers in medical device development, offering a decision support about the potential of medical devices to compete effectively in the market and generate profit. It could thus support successful portfolio management and project

prioritization, and lead to more informed resource allocation decisions within the company. However, further work is necessary regarding the actual use of the adapted model as a decision support in the early stages of medical device development.

Samenvatting

Het uitgangspunt van dit proefschrift is dat de ontwikkeling van nieuwe medische technologieën ondersteund kan worden middels vroege evaluatie van economische en klinische gevolgen van toekomstige implementatie. De inschatting van economische en klinische impact van een technologie kan ontwikkelaars en publieke instanties inzicht bieden in de toegevoegde waarde van de technologie. Evaluatie in de vroege ontwikkelingsfase is belangrijk, omdat juist in deze fase de technologie aangepast kan worden aan de eisen van de markt. Ook kan de ontwikkeling gestopt worden als de klinische meerwaarde van de innovatie te beperkt, de kosten van ontwikkelingen te hoog of de kans op vergoeding te klein lijken. Evaluatie van medische technologieën in de vroege fase zou kunnen resulteren in een kleinere kans op falen in latere ontwikkelingsstadia van de technologie, een grotere kans op implementatie en acceptatie in de praktijk en daarmee tot een toegenomen efficiency van research & development voor het bedrijf.

Aangezien het herhaald evalueren van medische technologieën gedurende de ontwikkeling relatief nieuw en onbekend is, zijn er nog veel vragen of de werkelijke meerwaarde en het gebruik door ontwikkelaars. Om deze vragen deels te beantwoorden, bevat dit proefschrift de volgende onderdelen:

1. Een verkenning van methoden om verschillende stakeholders te betrekken bij de evaluatie van klinische meerwaarde van een technologie,
2. Het bepalen van de kosten-baten verhouding van nieuwe technologieën, om daarmee de meest kansrijke technologieën te identificeren en de mogelijke economische rendement voor het bedrijf te bepalen,
3. Het ontwikkelen van een besliskundig hulpmiddel voor ontwikkelaars dat gebruikt kan worden om gedurende de technische ontwikkeling ook de klinische en economische aspecten in kaart te brengen.

In eerste instantie zijn in dit proefschrift de huidige stand van de wetenschap ten aanzien van methoden voor vroege technologie evaluatie in kaart gebracht (hoofdstuk 2). De resultaten van deze review laten zien dat vroege technologie evaluatie de potentie heeft om te leiden tot meer geïnformeerde besluitvorming, wat mogelijk zal leiden tot efficiëntere technologische ontwikkeling van hulpmiddelen met een succesvollere implementatie in de praktijk. Echter, er is geen gestandaardiseerd stappenplan voor vroege technologie evaluatie, wat het meten van de meerwaarde ervan moeilijk maakt.

De resultaten van dit literatuuronderzoek zijn vertaald in een vragenlijst om het huidige gebruik van deze methoden te onderzoeken (hoofdstuk 3). Dit onderzoek laat zien

dat hoewel op dit moment meerdere methoden voor vroege evaluatie in gebruik zijn binnen de medische hulpmiddelen industrie, er geen duidelijk overzicht en begrip is van hoe dit type onderzoek moeten worden uitgevoerd, welke voorwaarden er zijn voor de toepassing ervan en op welke manier de resultaten van dit type onderzoek het besluitvormingsproces binnen bedrijven ondersteund.

Op basis van deze resultaten van het eerste deel van dit proefschrift is de meerwaarde van een aantal veelbelovende methodieken getest op een aantal in ontwikkeling zijnde technologieën.

Om de mogelijke klinische toepassing en de impact van een technologie op de klinische praktijk te bepalen zijn mogelijke stakeholders (patienten, clinici, beleidsmakers) op een systematische manier betrokken bij de ontwikkeling van een point of care test voor nierfalen (hoofdstuk 4). Het betrekken van stakeholders in het ontwikkelingsproces van technologieën is een belangrijke eerste stap om behoeften te identificeren die leven in de doelgroep, alsmede om klinische, organisatorische en regulatoire hindernissen in een vroeg stadium te identificeren. Als zodanig zou het betrekken van stakeholders integraal onderdeel moeten vormen van het ontwikkelingsproces van nieuwe hulpmiddelen. Echter, de resultaten van het onderzoek beschreven in dit proefschrift laten zien dat op dit moment de mening van stakeholders slechts in beperkte mate invloed heeft op het ontwerp en de doelstelling van het toepassen van de technologie.

Om de levensvatbaarheid van een technologie in te schatten is voor een aantal technologieën, in verschillende stadia van ontwikkeling, het rendement op de financiële investering vanuit het perspectief van de ontwikkelaar en de verhouding tussen klinische baten en kosten van vergoeding vanuit maatschappelijk perspectief vergeleken (hoofdstuk 5). Vroege gezondheidseconomische modellering wordt gezien als een belangrijk onderdeel van een vroege evaluatie van medische hulpmiddelen. Hoewel er in traditionele gezondheidseconomische studies een focus is op het gebruik van complexe methoden voor kosten-effectiviteits analyse, lijkt het erop dat de headroom methode het beste aansluit bij de informatiebehoeften tijdens de vroege ontwikkelingsfase van een technologie. Daarnaast biedt de headroom methode de mogelijkheid de resultaten ervan te verbinden met het potentiële rendement op de investering en de meerwaarde van de technologie voor het gezondheidssysteem. Als zodanig is het implementeren van de headroom methode in vroege technologie ontwikkeling een eerste stap in de implementatie van “value based pricing” in de medische sector en in het bepalen van de commerciële

haalbaarheid van de ontwikkeling van nieuwe innovaties, al in de vroege fase van ontwikkeling.

De bevindingen van deze studies zijn tenslotte geïntegreerd in de doorontwikkeling van een generiek model dat wereldwijd gebruikt wordt voor de evaluatie van nieuwe technologieën. Dit model is aangepast aan de medische technologie sector. Het model kan gebruikt worden als een relatief eenvoudig besliskundig hulpmiddel, om gedurende de ontwikkeling van een nieuwe technologie op verschillende momenten de potentiële meerwaarde van de technologie op systematische wijze te evalueren, en de kans op succesvolle implementatie in te schatten. Het NewProd Model dat wordt voorgesteld in hoofdstuk 6 heeft de potentie zich te ontwikkelen tot een praktisch hulpmiddel dat ontwikkelaars kan ondersteunen tijdens de ontwikkeling van nieuwe technologische hulpmiddelen. Het NewProd model geeft informatie over de effectiviteit van de nieuwe technologie en de mogelijkheid voor het bedrijf om winst te maken middels de ontwikkeling ervan.

Daarmee kan het gebruik van een dergelijk model leiden tot meer succesvolle keuzes in de ontwikkeling van nieuwe technologieën, en het prioriteren van projecten, en daarmee kan het leiden tot een meer geïnformeerde verdeling van middelen binnen een bedrijf. Echter, meer onderzoek is nodig om de werkelijke meerwaarde van een uitkomsten van een dergelijk model bij het ondersteunen van besluiten binnen het bedrijf te onderzoeken.

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Katarzyna Markiewicz-Barreaux
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List of publications

JOURNAL PAPERS

Markiewicz K, van Til JA and IJzerman MJ. Medical devices early assessment methods: systematic literature review. *International Journal of Technology Assessment in Health Care*. 2014; 30(02): 137-146.

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Curriculum Vitae

Katarzyna Markiewicz was born April 13th 1983 in Poznan, Poland. She started her studies at the University of Life Sciences in Poznan in Poland, where she graduated with Bachelor Degree in 2007. In 2008 she completed her Bachelor Degree in International Livestock Production at Christelijke Agrarische Hogeschool in Dronten in the Netherlands. In 2010 she received her Master of Science Degree in Animal Breeding and Genetics (Major) and Business Economics (Minor) at Wageningen University in the Netherlands.

In May 2011 Katarzyna started to work as a PhD candidate at the department of HTSR (Health Technology and Services Research), on the project titled 'Development of the Twente Medtech Innovation Index'. The aim of the project was to develop an index, based on decision analytic modeling, to estimate the potential of new medical technologies, while in the same time to incorporate user preferences, clinical effectiveness, disruptive or incremental innovation and reimbursement of the technology in the index. The practical relevance of the study was in predicting the technology potential early in development, in a stage in which it can be adapted to fit the environment or the environment can be prepared for the technology or, if potential is very low, further development can be dismissed.

In November 2015 Katarzyna started working for the Koninklijke Philips N.V., a Dutch technology company in Eindhoven with primary division focused in the area of healthcare (Royal Philips). Katarzyna works in the Centre for Information Sciences as an Information Specialists.