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Maximizing the Value of Engineering and Technology Research in Healthcare: Development-Focused Health Technology Assessment

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This chapter focuses on three main topics. The first aims to provide an explanation of the principles of health technology assessment (HTA) and its familiar role in determining coverage of healthcare provision. Second, we discuss the growing contribution of HTA in the development and translation of medical devices introducing what we term "development-focused HTA"(DF-HTA). We set out the role of DF-HTA in identifying needs, assessing the potential of technologies in development, aiding design, and tailoring evidence generation activities. Finally, we outline the challenges of development and assessment presented by medical devices distinguishing large capital items, point of care devices, diagnostics, implantables, and digital devices. Each category of device has its own set of challenges for developers and HTA analysts alike. Challenges include a complex licensing and regulation environment, short lifespan and incremental improvement, difficulties in generating clinical evidence, the importance of contextual factors (e.g., how the device will be used and by whom), patient and clinician acceptance, and the indirect health benefit from diagnostic devices.

1.1 Introduction

Advancements in engineering and technology have the potential to revolutionise patient care and medical research. However, resources available for research and development and for healthcare provision are limited, so it is essential that any funds invested are spent on those projects that are both likely to succeed and likely to make a difference to patients' health. Health Technology Assessment (HTA) is a multi-disciplinary approach that studies the medical, social, ethical, and economic implications of development, diffusion, and use of health technology (INAHTA.ORG 2019). HTA has been most widely used by public payers or reimbursement agencies when a technology (such as a pharmaceutical or a medical device) is ready for market. However, there is increasing recognition that HTA undertaken at an earlier stage in the development of a health technology can aid investors and developers to focus their resources on technologies that are likely to succeed as well as identifying those that are likely to fail (IJzerman et al. 2017). We term this earlier form of HTA,

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"development-focused HTA" (DF-HTA) and the more familiar form of HTA "use-focused HTA."

Health technology is a broad term that encompasses drugs, medical procedures, tests, and service configuration. Medical devices form a sub-set of health technology. The diverse sub-set includes large, expensive, capital equipment such as the Da Vinci robotic surgery platform (INTUITIVE.COM 2019) and small consumable items such as sticking plasters. There are some common challenges for developers of all categories of medical device. In particular, the licensing and regulatory environment is highly complex and differs according to the jurisdiction where the device will be used. Evidence generation is also particularly challenging for many kinds of medical devices as different decision-makers require different levels of evidence. For devices with short lifespans, when it is common for different versions to be developed sequentially with incremental improvements, it is difficult to know which version of the device the evidence relates to. Items like the robotic surgery platform are subject to the "learning curve" effect, as surgeons need an initial training period to improve their competence before the clinical effectiveness of the new equipment can reasonably be compared with prior standards of care. Diagnostic tests form an important sub-category of medical devices. Evidence generation for diagnostics is challenging because any health outcome resulting from the use of the diagnostic is indirect rather than direct. In order for there to be an improvement in health, the diagnostic test needs to change the diagnostic or treatment pathway so that the patient is treated sooner or more effectively. Not only is any health gain indirect, it also depends upon the behavior of the clinician and the patient. A test may indicate that treatment B is more appropriate for the patient, but if the patient and/or the clinician prefer treatment A, the test cost has been wasted and the patient's health is not improved. The value proposition for many devices is also contextually dependent. By this we mean that the device may add value in some places but not others, depending on factors such as what the current treatment and diagnostic pathways are; staffing levels; capacity and workflow; and, what other capital equipment is in place.

The numerous challenges facing developers of medical technologies in general, and medical devices in particular, have led to a recognized problem in translating research from bench to bedside. One response to this has been the growth of translational research bodies charged with supporting developers and bridging the translation gap. Two notable contributors to the DF-HTA literature are the Center for Translational Molecular Medicine (LYGATURE.ORG 2019), based in the Netherlands and MATCH UK (MATCH.AC.UK 2018), a collaboration between several UK universities. This growing literature demonstrates how the various challenges of medical device development can begin to be addressed at an early stage of development using the methods of DF-HTA.

The aims of this chapter are to explain what HTA is and how it has been used to determine the coverage of healthcare provision; to explain what DF-HTA is and how it differs from use-focused HTA; to set out the challenges in the development and assessment of medical devices; and to illustrate the contributions of DF-HTA in the development and translation of medical devices through a number of case studies.

1.2 What Is HTA?

Healthcare resources are limited in every setting, and decision-makers are faced with difficult choices about which technologies should be adopted and used within their service. The definition of HTA given in the introduction (INAHTA.ORG 2019) was

> HTA is a multi-disciplinary approach which studies the medical, social, ethical and economic implications of development, diffusion and use of health technology.

Technology in HTA is widely defined and includes drugs, devices, health services, and systems. As the study of these various aspects of health technologies, HTA is well-placed to inform decision-makers as they make resource allocation decisions. Indeed, the role of HTA to inform decision-makers is included in the World Health Organisation (WHO.INT 2019) definition of HTA:

> the systematic evaluation of properties, effects and/or impacts of health technologies and interventions. It covers both the direct, intended consequences of technologies and interventions and their indirect, unintended consequences. The approach is used to inform policy and decision-making in health care, especially on how best to allocate limited funds to health interventions and technologies.

An ongoing project to reach a consensus definition of HTA proposed a definition that includes the important additional factors of a systematic and transparent process.

> a multidisciplinary process that uses explicit and scientifically robust methods to assess the value of using a health technology at different points in its lifecycle. The process is comparative, systematic, transparent and involves multiple stakeholders. The purpose is to inform health policy and decision-making to promote an efficient, sustainable, equitable and high-quality health system.

Health Technology Assessment, as a discipline, first developed in the United States when Congress requested Technology Assessment of health technologies in the mid 1970s (Stevens et al. 2003), and the term is now internationally used. The adoption of this term gained popularity in wealthier countries that prioritized the evaluation and improvement of health care. HTA draws on Evidence Based Medicine (EBM). EBM developed from the publication in 1972 of Archie Cochrane's "Effectiveness and Efficiency" (Cochrane 1972) and is now championed by the international organization, the Cochrane Collaboration (Stevens et al. 2003). Evidence synthesis methods such as systematic review and meta-analysis are core to HTA and draw heavily on guidance developed by the Cochrane Collaboration. These methods often form the basis for the clinical effectiveness estimates in cost-effectiveness analysis and health economic modelling.

The components of HTA vary according to the particular decision-maker, but many forms of HTA start with the definition of a decision problem to address. Analysts may find it useful to use a structure to help them define the decision problem. A popular structure is PICO, which stands for Population, Intervention, Comparator, and Outcome. The intervention is

the technology to be assessed, and the comparator is the current standard of care in that disease area. Once the decision problem has been defined, the next step is synthesis of the clinical evidence, using techniques such as systematic review and meta-analysis. Once the evidence on clinical effectiveness has been assembled and issues regarding evidence quality and generalisability addressed, cost-effectiveness can be considered. Finally, other considerations such as legality and ethics may be addressed (Eddy 2009).

HTA informs a variety of healthcare decision-makers, ranging from national healthcare providers like the National Health Service in the UK, to regional health authorities (for example, in Spain and Canada) and local providers such as hospitals. Insurance companies and commercial healthcare providers also need to make decisions about coverage and reimbursement. HTA agencies may be established within, or supported by, the decision-maker as with the National Institute for Health and Care Excellence (NICE) in the UK or may be external bodies such as the Institute for Clinical and Economic Review (ICER) in the United States, which is funded primarily by not for profit organizations (ICER.ORG 2019) and provides advice for guidance. Some agencies have a strong emphasis on cost-utility analysis (for example, UK, Netherlands, Canada) and some have acknowledged a financial limit to the amount they consider acceptable to pay for each year in full health delivered by a health technology.

Decisions supported by HTA include two broad categories: allocation of a set budget over a number of healthcare areas and decisions about individual technologies or programs. In the first category, the decisions involve which programs to include in a package of Universal Health Coverage (for example, maternity care, vaccination programmes) or decisions about prioritization within a research budget. The aim of the HTA would be to allocate the budget according to agreed criteria of effectiveness, value for money, and other considerations, perhaps equity. The second category includes assessment of individual technologies, such as pharmaceuticals, to determine whether they should be adopted. Again, they would be likely to be assessed against pre-established criteria relating to evidence base, need, value for money, and equity issues. Medical devices and surgical procedures could also be assessed in this way. HTA may also be used to determine whether a technology in current use should be excluded from reimbursement or coverage. This is known as "disinvestment." There is growing interest in how HTA could be used before or during the development of a technology to inform a broader set of decisions. This form of HTA, which we have termed "development-focused HTA," is the subject of the next section.

1.3 What Is Development-Focused HTA?

Development-Focused HTA (DF-HTA) is concerned with whether and how a technology should be developed. It is contrasted in this section with Use-focused HTA (described in the previous section), which compares the clinical benefit that an available technology is likely to deliver to the cost of the technology and makes a recommendation to a decision-maker based on an assessment of opportunity cost and other local criteria. DF-HTA differs in that the technology is under development, perhaps still at the concept stage. DF-HTA aims to inform the developers of the technology about a wider range of questions, including how the technology should be designed, used, and/or priced. DF-HTA is a relatively young but expanding field. We believe that the tools of DF-HTA could be usefully employed to evaluate technologies in development and ensure that only those that are likely to succeed continue

Table 1.1 Key Differences between Use-Focused and Development-Focused HTA.

Feature	Use-focused HTA	Development-focused HTA
Target audience	Reimbursement agencies, insurers, clinicians & patients	Technology developers, investors, and public sector funders
Specific decisions HTA designed to inform	One off Binary - accept/reject Optimising guidelines Price revisions Reimbursement decisions Budget allocation	Broad range including: Go/no-go decisions Technology design Trial design Research prioritization Reimbursement strategy prioritization
Available evidence	Evidence-base more developed	Evidence-base fluid, may be limited
Timing	Close to and post-approval	Repeated
		Pre- and during development
Underlying user objective	Maximize health	Maximize financial and/or societal return on investment
Core decision rule	Reimburse when value meets established criteria	Continue development if project has (most) potential to deliver financial/societal return on investment
Clinical decision space	Targeted at specific decision-makers, indications, comparator and patient groups defined by local practice and licensing	Potentially multiple jurisdictions, indications, comparators, funders, user, groups, thresholds (test cut-off), levels of test performance, and positions in pathway
Business model	Fixed, reimbursement by payer/insurer	Broad, not yet defined
Resources for analysis	Committed - limited number of technologies reviewed	Often constrained
Stance of analysis	Normative	Positive
Burden of Proof	Established standard of evidence	Evidence credible to the development team

to be developed as well as to prioritize research expenditure on new health technologies. This form of HTA, used to inform developers of health technologies, has been termed "early HTA" in the academic literature (Ijzerman and Steuten 2011). We prefer to use the label "development-focused HTA" as it is the audience, rather than the timing of the HTA, which drives many of the differences. Table 1.1 sets out key differences between use-focused and development-focused HTA, and these are explained in the paragraphs that follow using an example of home brain monitoring in epilepsy patients.

1.4 Illustration of Features of Development-Focused HTA

Digital health technologies have the potential to improve patient health through improved diagnosis and/or ongoing monitoring of health conditions. They may also reduce cost by accelerating diagnosis and/or reducing hospital admissions. The following paragraphs contrast a use-focused HTA exercise and a development-focused exercise concerning a

home-based brain monitoring device (HBM) for epilepsy patients. Epilepsy is diagnosed using electroencephalography (EEG), but because the standard routine of EEG is relatively short, it has only 20-56% sensitivity (Breteler 2012). HBM could increase the sensitivity of diagnosis to in excess of 90 percent by increasing the period of observation and adding a detection algorithm (Breteler 2012).

1.4.1 Use-Focused HTA

The timing of any use-focused HTA would be after the device was licensed when it was available for purchase. The audience for a use-focused HTA of HBM would generally be a national decision-maker (perhaps a ministry of health or a national reimbursement agency) but could potentially be a healthcare provider at a more local level, such as a hospital. The underlying objective of either of these decision-makers would be to maximize health given the budget at their disposal. The specific decisions to be informed would be whether to purchase the monitoring system and potentially, in which populations it should be used. Although the level of evidence required for a device to be licensed is not as well-defined as the evidence required for a pharmaceutical, the available evidence should include evidence of safety and performance. The analysts undertaking the use-focused HTA may find sufficient evidence of clinical utility or may flag up that some additional evidence is required prior to any decision being made. The price of the system would be known (although it may potentially be open to negotiation). The decision space in this exercise would be relatively narrow as the jurisdiction and disease are both fixed. It would probably be necessary to consider different sub-groups of the population where the effectiveness of HBM may vary and possibly different positions in the diagnostic pathway. A use-focused HTA of a diagnostic technology may involve modelling the impact of the technology (HBM) on health outcomes and resource use over a long time-horizon. This analysis would produce an estimate of the clinical efficacy and cost-effectiveness of the technology, which could then be used to inform the one-off decision about whether or not to purchase. This decision would be informed by the decision-makers' underlying decision rule in order to decide whether or not to implement the program. If a national decision-making body commissioned the HTA exercise, the resources available for analysis are likely to have been adequate to undertake a comprehensive analysis. However, for diagnostic technologies and other devices, use-focused HTA is sometimes undertaken by smaller, local healthcare services, and they may need to undertake a less comprehensive review to reflect the resources they have available.

1.4.2 Development-Focused HTA

By way of contrast, the timing of a development-focused HTA may precede the discovery research for a digital health application or may be undertaken when there is a prototype available but there are decisions to be made about whether it is worthwhile to continue the development or to prioritize its implementation. The target audience for the HTA analysis may be a public or charitable research funder allocating funds across a portfolio of projects or a commercial developer/investor. The underlying objective of these two groups would potentially differ with public or charitable research funders looking to maximize health given the budget at their disposal and commercial developers/investors looking to

maximize financial return on investment. The timing of the assessment would determine the available evidence, but this is unlikely to be large-scale technology-specific evidence even at the prototype stage. Evidence is more likely to come from bench studies, similar technologies, or assumptions informed by input from experts. In contrast to use-focused HTA, the decision space in this exercise may be very wide. There may be scope to use HBM in many different geographical areas, populations, and diseases. As in use-focused HTA, the analysis may involve modelling the health and cost impact of HBM, but a number of plausible scenarios may be modelled incorporating evidence and assumptions as described above. Modelling would be an iterative process, revised a number of times, reflecting evidence generated and with increasing sophistication as the decision-space became narrower through the development process. Rather than informing a single decision, the analysis informs ongoing discussions. Even if the analysis showed that the technology in the current form in the selected scenarios did not look promising, this may not mean that it should be abandoned - it may instead indicate that other settings are preferable or an improved design is required.

1.5 Activities of Development-Focused HTA

The features identified above drive important differences between development and use-focused HTA in the analytic tools used. Synthesis of clinical evidence and economic evaluation are the mainstay of use-focused HTA, as the assessment tends to focus on comparative effectiveness, cost-effectiveness, and budget impact associated with well-defined interventions. In contrast, development-focused HTA draws on a broad range of multi-disciplinary methods due to the wide range of the decisions that development-focused HTA is intended to inform. Development-focused HTA can be considered as contributing to iterative and interlinked assessments of clinical and economic value. The clinical value assessment considers what impact the technology might have on clinical practice and health (and wider social) outcomes. The economic value assessment builds on the clinical value assessment to consider the economic impact of changes in healthcare resource use and other economic value drivers such as productivity effects. It may also include consideration of the potential pricing of the new technology, volume of sales, fixed and variable costs of production and distribution in order to produce estimates of net margin. These assessments are informed by and in turn provide information to the research and development process and the business case for the technology (see Figure 1.1).

The arrows in Figure 1.1 indicate the complexity of the links between the aspects of the framework. Table 1.2 sets out examples of the links represented by the arrows, many of which are reciprocal. Rather than being bidirectional, clinical value assessment must necessarily precede economic value assessment as the change in clinical pathways forms the basis of any decision model. The relationship between these two assessments is, however, iterative as economic value assessment (informed by strategic and market analysis undertaken in business case development) may inform the selection of jurisdictions to be assessed in a clinical value assessment.

The relationship between the research and development process and clinical case assessment is reciprocal. Evidence generated in the research and development process is used to

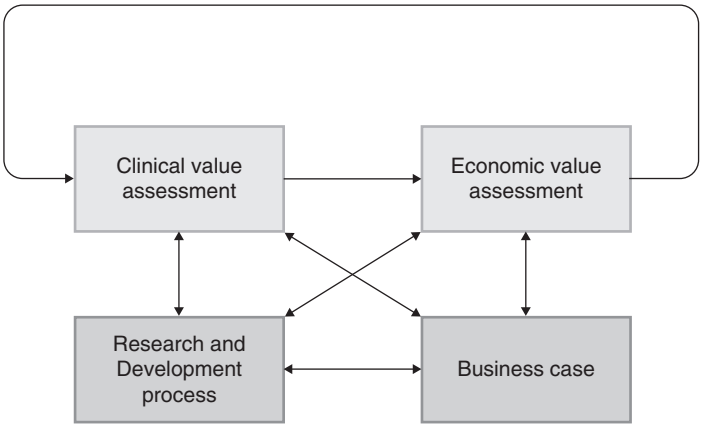

Figure 1.1 Activities of development-focused HTA.

populate the clinical value assessment. Where this evidence is not available (as in much early stage development-focused HTA), methods of evidence generation can be used to fill the gaps (see Table 1.4). It is important to distinguish research and development evidence generation (such as clinical trials and clinical trial simulation) and evidence generation to support the assessment process (such as expert elicitation and the use of estimates from the literature). The clinical value assessment informs the research and development process about the kind of evidence that is required for the assessment as well as providing insight into contextual aspects that may require building into the design and indicating target thresholds of performance for the technology to add clinical value. Business case development may feed target markets and indications directly into the clinical value assessment. The detailed epidemiological analysis involved in clinical value assessment may lead to better-informed estimates of the market size in the business case development.

Economic value assessment may inform the research and development process by using threshold analysis to determine the minimum performance characteristics for a technology to be clinically effective and cost-effective in a particular jurisdiction. Again, this relationship is reciprocal as the research and development process may inform the economic value assessment about the likely cost-profile of the technology. Economic value assessment also has a reciprocal relationship with business case development. Economic value assessment can contribute to pricing decisions as well as providing analysis as to the scale of potential diffusion-related issues. As the business case develops, this can narrow down the indications and jurisdictions to be targeted and forming the basis for the economic value assessment. The final reciprocal relationship shown in the proposed framework is that between the research and development process and business case development. The research and development process informs business case development about the potential indications that the technology could target as well as information about the cost profile of the technology and development costs. Business case development provides guidance to the research and development process about the thresholds for these cost parameters for the technology to be commercially viable.

Table 1.2 Examples of information flows represented by arrows in Figure 1.1

Arrow from	Arrow to	Information flow
Clinical value assessment	Economic value assessment	Clinical effectiveness of technology and comparator – multiple jurisdictions/indications, Contextual information to allow modelling of pathway changes, Insight into diffusion issues that may be included in modelling – e.g., importance of adherence
Economic value assessment	Clinical value assessment	Markets/indications with most economic potential
Clinical value assessment	Research and development process	Evidence gaps Threshold technology performance to improve clinical effectiveness Insights into contextual aspects requiring consideration in design
Research and development process	Clinical value assessment	Evidence of clinical effectiveness
Clinical value assessment	Business case development	Market size
Business case development	Clinical value assessment	Target markets and indications
Economic value assessment	Research and development process	Threshold technology performance for cost-effectiveness Evidence gaps
Research and development process	Economic value assessment	Cost profile of technology
Economic value assessment	Business case development	Pricing thresholds Insight on potential impact of diffusion-related parameters
Business case development	Economic value assessment	Target markets and indications for scenario selection
Research and development process	Business case development	Cost profile of technology – development and production Potential indications
Business case development	Research and development process	Thresholds for costs of production and development

1.6 Analytical Methods of Development-Focused HTA

Table 1.3 presents analytic methods of development-focused HTA that have been employed in undertaking the clinical and economic value assessments, as well as methods that have been previously classed as DF-HTA but which we would classify as either research and development or business case development. Table 1.4 presents methods of evidence generation for DF-HTA. We illustrate a selection of appropriate methods through the continuation of the HBM example and through the case studies that will be discussed later in the chapter.

Table 1.3 Analytical methods by framework aspect

Framework aspect	Analytical methods
Clinical value assessment	Epidemiological analysis Health impact assessment
Economic value assessment	Cost-effectiveness analysis (including cost-utility analysis, cost-consequence analysis, cost-benefit analysis, cost-minimization analysis, headroom analysis, probabilistic sensitivity analysis, and one-way sensitivity analysis) Value of Information analysis (including EVPI, EVPPI, EVSI)
	Multi-criteria decision analysis (Analytic Hierarchy Process)
Research and development process	Clinical trials Clinical trial simulation Bench studies User-centred design
	Technological forecasting based on epidemiological data
	Research and development portfolio management Failure and reliability analysis
	Technology profiling/uncertainty profile
	Brainstorming sessions
	Preliminary market research
Business case development	Strategic planning methods: PEST, SWOT
	Horizon-scanning
	Scenarios building and evidence profile
	Return on investment Soft systems methodology
	Payback from research analysis
	Real Options Analysis
EVPI	Expected Value of Perfect Information
EVPPI	Expected Value of Partial Parameter Information
EVSI	Expected Value of Sample Information
PEST	Political, Economic, Social, Technological
SWOT	Strengths, Weaknesses, Opportunities, Threats

Table 1.4 Evidence generation methods to support development-focused HTA

Method	Examples
Literature review/analysis	Archives, documents
Qualitative methods of user interaction	Focus groups, workshops, questionnaires, interviews, and surveys
Choice-based preference methods	Discrete choice experiments and conjoint analysis
Multi-criteria decision analysis	Analytic Hierarchy Process
Expert opinion and structured expert elicitation	Delphi method

1.6.1 Clinical Value Assessment

The clinical value assessment essentially compares clinical practice and outcomes in two or more future worlds: one without the new technology and one or more with (if there are multiple options for employing the new technology). The assessment of clinical value requires an understanding of the epidemiology of the disease, its current treatment and expected costs, and outcomes in the local context. This may be based on published epidemiological studies and published treatment guidelines, opinions from local experts, and, if feasible, local primary research. In all cases, it is crucial that the evidence be relevant to the setting(s) that we are interested in. In practice, this epidemiological analysis in relation to HBM would involve understanding the prevalence of relevant diseases, sub-types, and populations affected in a variety of geographical locations. Information required would be the number of patients affected, the impact on their health, and the current diagnostic and treatment pathways. These may be many and various depending upon the context. Practical considerations may require a narrowing of the settings investigated in-depth, although it is useful to have an overview of all potential relevant areas.

Next, a health impact assessment of the potential impact of the technology on the disease and treatment pathway will be required. In development-focused HTA, where there is likely to be a paucity of trial data or other empirical data relevant to the new technology, alternative methods of evidence generation are often required. These are described in the Evidence Generation section below. For HBM, we would need estimates of the technology's clinical performance in different positions in the diagnostic pathway (e.g., its ability to correctly identify epilepsy). We would also need to consider how the information from the test changed the diagnostic and treatment pathways and what impact this had on overall health outcomes (i.e., the clinical utility of the technology). An initial health impact assessment may make a range of estimates of clinical performance, including a perfect technology with 100% epilepsy patients identified. This assists developers in setting the boundaries for performance and/or price required for the technology to be clinically efficacious and/or cost-effective.

It is important also to note that new technology may offer incremental value in many ways, each of which may be valued in a different way by different users or other stakeholders. A technology may directly improve health outcomes, may facilitate service, and process improvements and/or reduce resource use. There may, for example, be value in a technology that is not as effective as the current standard of care but can be delivered in areas where the power supply is inconsistent. Ease of operation is another aspect of value that may need to be taken into account. Technologies may add value through being light and portable, using readily available consumables or having no requirement for the user to be literate.

1.6.2 Economic Value Assessment

The economic value assessment extends the clinical value assessment by accounting for healthcare and other resource usages. It may also include productivity and other wider impacts. In use-focused HTA, economic evaluation is typically undertaken to determine whether the technology, at a given price and given current evidence, represents a cost-effective use of healthcare resources. In development-focused HTA, economic evaluation plays a different role. It is used to support a range of decisions including whether further development should be funded and how studies should be designed.

Cost-benefit, cost-utility, cost-effectiveness, cost-consequence, and cost-minimisation analysis (Drummond et al. 2015), are all forms of economic value assessment in that all compare the difference in outcomes brought by new technology to the difference in costs. All methods calculate costs in the same way; however, they measure outcomes differently. In a cost-benefit analysis, outcomes are measured in monetary terms. The principal challenge is determining how the outcomes should be valued. In a cost-utility analysis, outcomes are expressed in quality-adjusted life years (QALYs) or disability-adjusted life years (DALYs). This form of economic evaluation is preferred in the Gates Reference Case for Low and Middle Income Countries (LMIC) (Claxton et al. 2014). This is because the outcome measures, QALYs and DALYs, used in cost-utility analysis are generic measures that facilitate comparisons across technologies and disease areas. In cost-effectiveness analysis, outcomes are expressed as a single disease-specific measure: for example, cost per infection avoided. In cost-consequence analysis, outcomes are expressed across multiple measures. A particular challenge with both these forms of analysis is the difficulty in making comparisons between indications and determining an acceptable threshold for willingness to pay. Finally, in cost-minimization analysis, it is assumed that outcomes are either equal or superior with the new technology, and hence it is sufficient to simply compare costs. The challenge with this analysis is that it is only appropriate when it is safe to assume that outcomes are either equal or superior with the new technology.

Cost-effectiveness analysis may be used in development-focused HTA in two main ways. It can be used to indicate whether a technology is likely to be regarded as cost-effective, and hence used at a given price for the new technology. Alternatively, it can be used to estimate the maximum price at which the new technology is likely to be deemed cost-effective. This has been referred to as ”headroom” analysis (Chapman 2013). Where these analyses are based on cost-effectiveness or cost-utility analysis, an estimate of an acceptable threshold willingness to pay will be required. A threshold of three times a country’s per capita Gross Domestic Product (GDP) has historically been used in LMICs. However, research is ongoing to determine values for the acceptable threshold that better reflects the opportunity cost of “shadow price” of investment in other healthcare technologies. Threshold analysis is a similar formulaic approach, which assumes a price for the technology and then investigates what values the other parameters need to take in order for the technology to remain cost-effective. These approaches are very simple and quick to perform and can be based on expert opinions or assumptions so they are ideal for undertaking extensive scenario or sensitivity analysis. Any factors that are not modelled can be assessed qualitatively alongside the simple modelling (Chapman 2013). For example, in the assessment of a diagnostic test for hepatitis C in development, (Chapman 2013) discussed the potential impact of a move away from routine testing by biopsy, which could limit the market for the new test. Scenario analysis examining different settings (for example, high/low prevalence and urban/rural setting) and varying sensitivity and specificity in local settings can be undertaken.

In addition to providing information about the potential economic value of a new technology, cost-effectiveness analyses can be used to provide estimates of the potential value of additional information from further research. This is known as Value of Information (VOI) analysis. The analysis can be used to estimate the net impact on health benefit arising from an increase in the probability of selecting the optimal treatment resulting from further research reducing uncertainty. VOI can aid study design and investment decisions (Vallejo-Torres et al. 2011).

In our example of a development-focused HTA of HBM, a number of scenarios would be worth considering. If commercial developers were developing HBM, they may use a form of headroom analysis based on cost-utility analysis to estimate the price they may be able to charge for the technology in order for it to remain below an acceptable cost-effectiveness threshold. They could use threshold analysis to determine what clinical performance would be needed to justify a given price. They could use value of information analysis to design clinical trials which address the areas of most uncertainty (Vallejo-Torres et al. 2011; Wong et al. 2012; Meltzer et al. 2011). A cost-utility analysis undertaken to inform a charitable or public sector funder may assume a price sufficient to cover the ongoing unit cost of the technology and then calculate the incremental cost-effectiveness ratio of different positions in the diagnostic pathway or different diseases. If the development of the technology seemed likely to have an acceptable incremental cost-effectiveness ratio (i.e., to deliver sufficient health impact for its cost), then the project should be continued. If it is too expensive, developers may need to try to alter the design to improve effectiveness or acceptability to patients and clinicians. VOI analysis has been used in a number of research prioritization pilots to help funders choose which clinical trials to fund (Bennette et al. 2016; Carlson et al. 2013; Meltzer et al. 2011). Alternatively, the results of the cost-utility analysis may form part of a multi-criteria analysis for project prioritization or the basis for a calculation of societal return on investment.

The economic analysis can be broadened to consider financial return on investment (ROI) and/or social return on Investment (SROI). ROI is used by commercial entities to estimate the likely return on a project and to determine whether to continue the project or not. The basic calculation is: expected revenues; less ongoing costs of production/distribution; less development costs still to be incurred. The commercial viability of a candidate technology will depend on combinations of price and volume that are achievable, fixed and variable costs of production, and development costs (Meltzer et al. 2011). The price or cost estimates from the headroom calculation can be multiplied by the expected volume of sales (from epidemiological analysis) to calculate revenue. SROI is a framework for measuring and accounting for a broader concept of value; it considers aspects valued by different stakeholders, such as reductions in inequality, environmental degradation, and improvements in well-being by incorporating social, environmental and economic costs and benefits (SOCIALVALUEUK.ORG 2019). Gains are typically measured in monetary terms (financial ROI) or can also be expressed in terms of social values. Costs remain the same in both cases. A societal return on investment analysis can be undertaken from multiple stakeholder perspectives (patient, society, manufacturer). Both ROI and SROI can be used as a means to prioritize projects within portfolios generally as input to a multi-criteria process. For example, a research team looking at investments in the development of biomarkers in the prevention of type 2 diabetes considered attributes including reduction in downstream costs, added quality-adjusted survival, cost of test, feasibility of treat-all option, competition and ease of implementation in an MCDA exercise (de Graaf et al. 2015).

Scenarios-building involves the development and consideration of multiple scenarios reflecting uncertainties about the context and future events. These scenarios could inform stakeholder analysis and be built in to future economic evaluation in order to provide a range of options for consideration throughout the development process (Joosten et al. 2016). This is a good illustration of development-focused HTA's role in informing discussions and decisions throughout the development process.

1.6.3 Evidence Generation

The assessments involved in development-focused HTA may involve consultation with a wide range of stakeholders including patients, physicians, and policy-makers. In the very early stages, evidence may be primarily based on literature review and consultation with the technology development team. Consultations with stakeholders may involve informal or formal qualitative methods such as focus groups or interviews, or may take the form of structured expert elicitation. Informal methods are appropriate (and may be the only option) when resources are limited. A particular concern in expert elicitation is that estimates are often too optimistic (particularly if the expert is involved with the development team) and under-represent uncertainty. Thus, formal methods have developed that attempt to address this concern. Formal methods can be divided into two main groups: structured expert elicitation (SEE) and multiple criteria decision analysis (MCDA). SEE is used to obtain estimates of relevant population parameters, for instance, what is the expected treatment effect for a new technology. MCDA provides a solution to a decision-problem, for instance, which is the optimum choice among a set of treatment options with different characteristics. Delphi methods are commonly used to elicit expert opinions and typically involve two rounds of questions to individual experts (Gosling 2014). In the first round, experts respond without knowledge of other responses. Responses are then shared and a second round of estimates is sought from the entire group. Estimates may include probability distributions or ranges. It is possible to compensate for optimism-bias and under-estimation of uncertainty through sensitivity analysis in economic evaluation or qualitative consideration of a broader range of options in scenario analysis. Responses may also be weighted according to experience in the field. Best practices for the conduct of expert elicitation are discussed by (Iglesias et al. 2016). Several on-line tools are available including SHELF (Gosling 2018) and MATCH uncertainty elicitation (Morris et al. 2014). The availability of these tools will aid the conduct of expert elicitation if resources are limited. Structured methods of expert elicitation have been used to: identify current treatment pathways and standard of care (Davey et al. 2011); to specify the technical features of current technology (Terjesen et al. 2017); to estimate likely levels of test performance (Haakma et al. 2011); to estimate treatment effect (Girling et al. 2007; Ostergaard and Mldrup 2010); to estimate the effect of a new test on discharge rates (Kip et al. 2018); and to consider the likely position of a test in a diagnostic pathway (Breteler 2012).

Multi-Criteria Decision Analysis (MCDA) describes approaches that seek to take explicit account of multiple criteria in a decision-making process (Wahlster et al. 2015). In the context of development-focused HTA, experts will typically be asked to indicate their preferences between current and one or more versions of the new technology. A set of criteria relevant to the decision problem will be identified. Each option will be scored on each criterion. Then, in consultation with the experts, weights will be assigned to each criterion and some form of aggregation conducted to identify the optimum treatment. MCDA techniques have been used to support development-focused HTA in various ways. Several studies have used the techniques to support design decisions through the assessment of the relative importance of features concerning safety, ease of use and aspects of performance (Hilgerink et al. 2011; Hummel et al. 2012). Analytic hierarchy process (a form of MCDA) has also been used to predict the health economic performance of a new surgical technique and populate

performance criteria for a diagnostic technology in development (Koning 2012). The MCDA process described by Koning established that the technology under development, an electronic nose for the diagnosis of infectious disease, was not sufficiently accurate or rapid to offer advantages in well-resourced settings but may be viable in lower-resource settings. Another use of MCDA has been to generate the criteria and key issues for two key stakeholder groups in the development of computer chips simulating organ functions for use in biotechnology development (Middelkamp et al. 2016).

1.7 What Are the Challenges in the Development and Assessment of Medical Devices?

1.7.1 What Are Medical Devices?

The term "medical device" includes a diverse range of medical technologies. The definition from the European Union device regulation (2017/745 2017) defines a medical device as:

> Any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the following specific medical purposes: i) diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease; ii) diagnosis, monitoring, treatment, alleviation of or compensation for, an injury or disability, iii) investigation, replacement or modification of the anatomy or of a physiological or pathological process or state iv) providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, or in or on the human body, but which may be assisted in its function by such means. The following devices shall also be deemed to be medical devices: v) devices for the control or support of conception; vi) products specifically intended for the cleaning, disinfection or sterilisation of devices.

This definition is from EU regulations governing the licensing of medical devices (2017/745 2017). It is notable that the definition is quite wide but specifically excludes technologies that achieve their treatment effect by pharmacological, immunological, or metabolic means. This excludes drugs and vaccines as they have separate regulatory provisions. The U.S. Food and Drug Administration also regulates medical devices, and their definition is similar to the European definition.

Medical devices include several key categories such as large capital items, point of care devices, diagnostics, implantables, and wearable/digital devices. Examples of large capital items are a Da Vinci Robotic Surgery machine or a Magnetic Resonance Imaging (MRI) Scanner. These items have a large upfront capital cost and may be in use for a number of years. They may be used across different disease areas. Point of care (POC) devices take a service previously delivered in a laboratory setting, such as a blood test and deliver it at the point of care, which may be the bedside in a hospital ward or in a remote, rural healthcare center in an LMIC. Often POC tests are less accurate than laboratory tests but have the

benefit of reaching more patients or being quicker with results. Diagnostics are tests that provide information and are broadly divided into in vivo diagnostics and in vitro diagnostics. In vivo diagnostics examine the body of the patient directly - for example, by monitoring blood pressure using a standard cuff. In vitro diagnostics take a sample of patient tissue or fluids and examine it in a laboratory environment - for example, the breast cancer prognostic test, Oncotype Dx, analyses a sample of tumor tissue in the laboratory and using an algorithm predicts whether or not a patient's breast cancer is likely to progress (ONCOTYPEIQ.COM). Implantables are devices that are directly implanted into the patient's body such as cardiac pacemakers. Wearable or digital devices are devices worn by, or implanted in, individual patients, which monitor symptoms or provide some therapeutic agent. An example of a wearable device is a subcutaneous insulin infusion or insulin pump that is implanted in a patient and delivers a constant level of insulin to a patient from an in-built reservoir.

1.7.2 Challenges Common to All medical Devices

1.7.2.1 Licensing and Regulation

Licensing and regulation of medical devices is highly complex and differs according to jurisdiction. The two main regulators of medical devices are the U.S. Food and Drug Administration (FDA) and the European Union (EU). Requirements for licensing in both Europe and the United States differ from those in place for pharmaceuticals. The level of evidence required for devices depends upon the classification of the device, hence the first hurdle for the developer is to understand which class their device is likely to fall into. In both the United States and the EU, devices other than in-vitro diagnostics are classified from Class I to Class III with Class III being the higher risk devices. For in-vitro diagnostics the categories are A-D.

In this paragraph, we use the EU to illustrate the complexity of licensing of medical devices. The United States has similarly complex requirements. In the EU, following classification of the medical device, it must undergo a conformity assessment, which involves the comparison of the device against essential requirements set out in the European Directives (EU 2017 745 and 746). The requirements cover issues such as whether the benefits outweigh the risks and whether the device achieves the claimed performance. Additional requirements cover chemical, physical, and biological properties, construction and environmental properties, potential contaminants, radiation protection, and the information to be supplied with the device such as instructions for use. The conformity assessment must include a clinical evaluation that demonstrates conformity with the relevant general safety and performance requirements, an evaluation of undesirable side-effects, acceptability of the benefit-risk ratio, and sufficient clinical evidence. The onus is on the manufacturer to decide and justify the level of clinical evidence necessary, which must be appropriate for the characteristics of the device and its intended use. At a minimum, a clinical evaluation must include a review of available clinical evidence in relation to the device in its intended use. Manufacturers must identify gaps in the evidence through a systematic literature review, which must be thorough and objective and include both favorable and unfavorable data. The depth and extent of the evaluation must be proportionate and appropriate to the nature, classification, intended purpose, and risks of the device. Novel and higher risk devices could

be subject to additional clinical review by an expert panel. Clinical investigations must be performed for all implantable devices and Class III*.

Following successful conformity assessment, the device can receive a Conformité Européene (CE) Mark and be marketed anywhere in the EU. Manufacturers must undertake post-market surveillance and vigilance. Post-market surveillance is preventative and proactive, and charges the manufacturer with ensuring the ongoing safety of the device and that an appropriate risk-benefit balance is maintained. Vigilance is reactive and includes reporting of serious incidents with elements of voluntary and mandatory reporting.

Evidence requirements are lower, in both the EU and the United States, if it can be demonstrated that the new device is essentially the equivalent of an existing device. The Medical Device Regulation (EU 2017/745) has tightened up the definition of equivalence including three aspects, technical (design, specifications and physiochemical properties), biological (materials, duration of contact, release characteristics), and clinical (same stage or severity of disease, same site, same population, kind of user). It is also required to have contractual access to all technical documentation for the equivalent device on an ongoing basis for high risk devices and sufficient access for all other devices.

Class III devices require the clinical investigation to be a primary investigation if a claim of equivalence is not being made. In the United States, for non-equivalent devices falling into Class III and all implantables, primary clinical data is expected for the pre-market approval process. For equivalent devices, the lighter process is known as pre-market notification or the 510k process.

Evidence requirements for devices are not as well established as for pharmaceuticals, and it is advisable for developers to contact the regulators early in the development process for advice. In the UK, the Medicines and Healthcare Products Regulatory Agency, an executive agency of the Department of Health encourages manufacturers to contact the Innovation Office early in the development process to seek advice on regulatory requirements and manufacturing processes. It is also useful at this point to consider whether the evidence required by organizations who may adopt the device differs from that required for licensing in order that both sets of requirements are taken account of in designing the evidence generation plan.

1.7.2.2 Adoption

Once the device is licensed, the challenge for the developer is to secure sales in one or more jurisdictions. The relevant decision-maker will vary depending on the device and the context. For large capital equipment, the hospital will often be the decision-maker, whereas for a diagnostic test, the decision may be made at the regional or national level. For some devices there will be multiple layers of decision-makers. Some medical devices will be sold directly to patients or individual primary care practices. Each decision-maker may require a different level of evidence.

For example, a hypothetical diagnostic test is licensed according to EU regulations and can now be marketed in the UK. The developers can sell the diagnostic test directly to patients, but the market for this is likely to be small in a country with free, universal health care. The test could be sold to primary or secondary care providers directly, but they are unlikely to adopt it widely without the endorsement of the reimbursement agency, NICE. NICE has two separate assessment streams for diagnostics. The Diagnostics Assessment

Programme (DAP) assesses diagnostics that are likely to add cost and improve health. DAP uses methods similar to the mainstream Technology Assessment program for pharmaceuticals in that it compares the incremental benefit from using the test with the incremental cost and compares the consequent Incremental Cost-Effectiveness Ratio to a pre-established threshold. If the test offers value for money, it is likely to be recommended although not mandated (as a pharmaceutical would be after a successful TA process). The other stream of assessment is the Medical Technology Assessment Programme (MTAP), which assesses simpler technologies that offer cost savings compared to existing care. Again, if the diagnostic is recommended, it is not mandatory for the National Health Service (NHS) to adopt it although NICE do issue guidance to the NHS to try and encourage diffusion of innovation. However, due to contextual factors (such as what testing the local laboratory already undertakes, existing diagnostic and treatment pathways) each locality will need to assess whether the NICE conclusion applies to their context. Budgetary considerations are also likely to come into play where adoption of the device is not mandatory.

For some categories of device, additional guidance on the evidence required for recommendation may be available. This is the case for digital health technologies in the UK. In March 2019, NICE issued the Evidence Standards Framework for Digital Health Technologies (DHT) (NICE.ORG.UK) that sets standards of evidence for effectiveness and for economic evaluation. The Framework separates DHT into three tiers and sets the minimum and best practice evidence requirements for each tier. Tier 1 DHT is the lowest risk category and comprises devices that provide services to health and social care professionals and do not include any measurable patient outcomes. The evidence required to establish effectiveness involves demonstrating the credibility, reliability, and acceptability of the DHT with UK Health and Social Care professionals and evidence of accurate and reliable measurement and transmission of data, if applicable. The evidence requirements are cumulative in that higher tier devices need to fulfil all the requirements of lower tiers and their own requirements. For the highest-risk devices in Tier 3b (devices providing treatment or active monitoring of a patient's condition) the minimum required is a high-quality intervention study (either experimental or quasi-experimental) showing improvements in condition-specific outcomes or behaviors using a UK-relevant comparator. Again, recommendation by NICE on the provision of this evidence does not guarantee adoption, and further evidence may be required by local decision-makers.

1.7.2.3 Evidence

As we explained above, it is difficult to know what evidence is required for regulation and adoption of medical devices. Further difficulty arises in evidence generation due to the nature of some medical devices, which make randomized controlled trials (RCTs) difficult. For example, blinding is an issue in some trials of surgical devices. Although it is possible to set up trials using sham procedures, this adds complexity and expense to evidence generation. Recruitment in trials can also be difficult when invasive treatments are involved. Devices can be used as soon as they are licensed, and the evidence required to obtain a license sometimes falls short of the evidence some adopters require. As devices start to be used in some areas, developers may be disincentivised to generate evidence, or it may be more difficult to conduct controlled research if a device begins to replace its comparator technology. Policy-makers have a difficult balancing act as they do not want to delay the diffusion of a beneficial medical device by requiring onerous levels of evidence, but they need to ensure the safety of devices in the light of high-profile product recalls of breast

implants and metal on metal hip replacements. Interestingly, the United States has higher evidence standards for licensing than Europe and also has less product recalls (Hwang et al. 2016). What is not clear is the opportunity cost of the delay in beneficial devices reaching the market.

1.7.3 Challenges Specific to Some Categories of Device

1.7.3.1 Learning Curve

Clinical outcomes often depend upon the training, competence, and experience of the clinician using the device. An RCT comparing a new device with a standard procedure may be demonstrating the difference between experience with the old procedure and inexperience with the new, rather than differences between the procedures themselves. This phenomenon is known as the learning curve. It needs to be taken account of in evidence generation to ensure that evidence from different centers and clinicians is comparable and reflects the potential of the device. Evidence generation strategies to avoid distortion by learning curve effects include setting trial criteria specifying a minimum level of previous operations, standardizing the level of experience of the centers, using statistical techniques to identify outcomes likely to be associated with learning curve or adjusting primary outcomes for a probable learning curve effect (Conroy et al. 2019; Papachristofi et al. 2016). A 2019 review of surgical trials in leading journals found that this is not routinely done and is poorly reported (Conroy et al. 2019).

1.7.3.2 Short Lifespan and Incremental Improvement

Medical devices are hard to evaluate as evidence is often generated on a range of models that are incrementally improved over a relatively short lifespan. Evidence may be generated on a range of devices that are being upgraded and changing capability. In addition to issues with clinical effectiveness evidence, prices may also change dramatically due to the market entry of new products, modifications, or volume discounts. Both factors mean that a technology appraisal could be outdated before it is completed.

1.7.3.3 Workflow

Many medical devices are dependent for their clinical efficacy and cost-effectiveness upon the context in which they are used and how they impact the current workflow. For example, an imaging device that was able to exclude malignant melanoma would only reduce the workload of specialist dermatologists in areas where those specialists currently saw all patients rather than in areas where some form of remote triage (for example, teledermatology) was already undertaken. Developers need to understand the workflow and user needs in all target settings in order to understand the clinical and economic value of the device. Devices that are disruptive, in the sense that they require re-engineering of workflows or investment in infrastructure, for example, will face greater barriers to diffusion.

1.7.3.4 Indirect Health Benefit

Diagnostic tests do not deliver health benefit by themselves. They improve health outcomes only if treatment changes because of the test result. As well as making evidence generation difficult, this results in cost savings potentially being realized in a different place in the

clinical pathway. For example, part of the value proposition of Oncotype Dx, a commercially available prognostic test for patients with breast cancer is that chemotherapy costs will be avoided for a number of patients. Where the payer is an insurance company all incentives are aligned as the decision-maker that buys the test also pays for the chemotherapy. In other healthcare systems, the budget holder for diagnostic tests may be different from the drugs budget holder and incentives are not aligned. Awareness of the various incentives is essential for the developer in order to effectively market a diagnostic test.

1.7.3.5 Behavioral and Other Contextual Factors

The treatment effect of a medical device can be influenced by the preferences of both patients and clinicians. This makes generation of clinical evidence very challenging, as traditional randomized designs struggle to separate the impact of preferences and the treatment effect of the device. Potential solutions are innovative clinical study designs that take into account patients and/or clinicians' preferences (for example, the comprehensive cohort design (AbdElmagied et al. 2016) and qualitative studies. Developers of medical technologies must interact with potential users of their technology at an early stage of development so that they understand the impact of users' preferences.

1.7.3.6 Budgetary Challenges

As well as potential misalignment of incentives for diagnostic tests, other categories of device face budget challenges. Large capital items require upfront payment although developers may consider flexible business models that allow payment to be restructured. Implantable devices that offer longer lifespans also require investment upfront to save costs later, which may not be appealing to some payers.

1.8 The Contribution of DF-HTA in the Development and Translation of Medical Devices

It has been recognized internationally that the challenges faced by developers of medical devices are daunting. Delays in translation result in promising technologies not being available to improve the health of patients on a timely basis. In response to these challenges translational research bodies have been established with the aim of closing the translation gap. Two of the most active bodies in terms of published DF-HTA have been the Center for Translational Molecular Medicine (Steuten 2016) from the Netherlands and MATCH UK (MATCH.AC.UK 2018) a collaboration of UK universities. The following case studies are drawn from their portfolios with the exception of Kolominsky-Rabas et al. (Kolominsky-Rabas et al. 2015), which introduces the ProHTA project from Germany. The MaRS Excellence in Clinical Technology Evaluation (EXCITE) program in Canada (Levin 2015) is also worthy of note (MARSDD.COM 2019). MaRS EXCITE forms a model that European Healthcare Leaders are seeking to emulate where clinical trials are co-designed by developers and licensing and reimbursement authorities, and parallel submission to the authorities is encouraged (Ciani et al. 2018).

The case studies illustrate the role of DF-HTA in informing a broad set of decisions faced by developers of medical devices.

1.8.1 Case Study 1 - Identifying and Confirming Needs

This case study concerns an innovative laparoscopic instrument in development (Kluytmans et al. 2019). The developers initially thought that the instrument would improve various surgical procedures including meniscus surgery by replacing a number of different instruments in one, optimizing operating conditions for the surgeon and reducing the risk of infection thus improving patient experience and outcomes. The DF-HTA used a combination of qualitative stakeholder input to undertake a clinical value assessment followed by an economic value assessment using threshold and headroom analysis. The results of the qualitative exercise found that clinicians and other stakeholders, while enthusiastic about the new technology, felt that it did not offer significant incremental benefit over the current technology in the indication identified. A negative result is particularly valuable to developers as it allows them to refocus on a clinical area where there is more potential before significant expenditure has been incurred.

1.8.2 Case Study 2 - What Difference Could This Device Make?

ProHTA is an ambitious German project that uses a complex simulation model to assess technologies in development to see what clinical impact they may have and what characteristics the technology requires in order to deliver that performance. Kolominsky-Rabas et al. 2015 describe the application of the model in assessing Mobile Stroke Units. The units offer clinical value as they potentially reduce time to thrombolysis, thus improving patient outcomes. The simulation model demonstrated that the mobile stroke units save up to 49 minutes between the ambulance call and the therapy decision, and that this is enough to move 16.4 percent of patients into the most favorable time interval for thrombolysis.

1.8.3 Case Study 3 - Which Research Project Has the Most Potential?

This case study reports a multi-criteria decision analysis (MCDA) approach to clinical and economic value assessment in order to prioritize potential research projects in CTMM (de Graaf et al. 2015). The goal of the MCDA was to identify the biomarker project with the most potential to reduce the burden of Type 2 diabetes. The first step involved the identification of six criteria for the assessment from discussion with decision-makers. Criteria included three relating to barriers to realize potential and three concerning cost and impact on quality of life. The second step involves scoring each alternative project on the six criteria (either numerically, where this can be estimated or ordinally). The third step calculates the preferred option, making different assumptions about the weighting of the different criteria. The process allowed the developers to exclude one of the four research options regardless of decision-maker preferences and to rank the other three dependent upon whether the decision-maker prioritizes financial criteria or ease of implementation.

1.8.4 Case Study 4 - What Is the Required Performance to Deliver Clinical Utility?

In another case study from CTMM, Buisman et al. (2016) undertook a clinical and economic value assessment of four diagnostic tests for rheumatoid arthritis (B-cell test, IL6

test, imaging of hands and feet, and genetic assay). The tests were assessed using a five-year health economic model in the form of a decision tree followed by an individual-level state-transition model. The study illustrates the complexity of diagnostic assessment as it models each test in two different places in the current diagnostic pathway and in different sub-populations based on the risk of RA. There was much uncertainty around costs and estimates of test performances, as is usually the case in DF-HTA, but the study was able to identify a likely dominant strategy (the B-cell test) and determine the cost and test performance required for the preferred option to be cost-effective (EUR 200-300. High specificity).

1.8.5 Case Study 5 - What Are the Key Parameters for Evidence Generation?

Vallejo-Torres et al. (2011) carried out a three-stage economic evaluation of absorbable pins for Hallux Valgus compared to sutures and metallic pins. The early stage used headroom analysis to prioritize competing products, the mid-stage began to synthesize available data into a decision model, and the final stage developed a full decision model. The mid-stage model allowed the exploration of uncertainty and the identification (through Value of Information analysis) of those parameters for which further information would be most valuable. The study found that quality of life data was the most valuable data to collect in the next stage of evidence generation.

1.9 Conclusion

Although engineering and technology have the potential to revolutionize patient care and health outcomes, there is evidence of much waste in healthcare research (Greenhalgh et al. 2018). There is a tendency for research to be technology led rather than needs led (Kluytmans et al. 2019) and evidence that funding for enterprising firms in health technology is not always aligned with health research funding streams (Lehoux et al. 2017). Evidence suggests that many developers of medical devices do not use formal methods of decision-support and do not have in-house capacity and knowledge to perform HTA (Craven et al. 2012; Markiewicz et al. 2017). This, despite the immense challenges faced by developers of medical technologies, particularly in evidence development, licensing, regulation, and adoption.

The case studies described above suggest that there are benefits for developers in consulting an HTA practitioner at an early stage in the development process. The most immediate benefit is that the HTA is able to inform a go/no-go decision at any point in development. The first case study demonstrated that there was little potential value in pursuing the project if the target was meniscus surgery. This negative finding is extremely useful to developers, who can then focus their efforts in other clinical areas. Where the indication was that the project had potential clinical utility, as in the other four case studies, DF-HTA offers benefits. In the second case study, the simulation model demonstrated to external stakeholders the potential utility of the Mobile Stroke Units in the specific context of the German healthcare system. The third case study allowed the exploration of decision-makers' criteria and understanding of the relative priority of the projects dependent upon the weighting between

them. It also allowed the rejection of one of the alternatives regardless of the weighting between criteria. This prioritization took place before significant expenditure on any of the biomarker projects illustrating the usefulness of DF-HTA in avoiding research waste. The fourth case study illustrates the complexity of a contextual analysis of diagnostic tests that would be difficult for many developers to undertake without the support of a translational research body like CTMM. The useful information generated from this exercise allowed the prioritization of the B-cell test, which dominated in most modelled scenarios and provided the developers with guidelines as to the performance and test costs required in order to make the test cost-effective in the Netherlands. The final case study demonstrated the iterative nature of DF-HTA and showed how earlier stages of analysis can guide evidence development in later stages, indicating which are the most important parameters for cost-effectiveness.

DF-HTA has a role to play in maximizing the potential of development in science and technology. DF-HTA can help ensure that medical devices in development meet a clinical need and deliver clinical utility in the context in which it is hoped they will be used. They can alert developers at an early stage where a device is unlikely to make a difference and provide information about how good the device has to be to make a difference. Undertaken early in the device development process, evidence generation can be tailored to ensure that it meets the needs of licensing and reimbursement agencies. As is clear from the case studies, translational research bodies that facilitate links between commercial entities, academic and clinical researchers, clinicians, regulators, and reimbursement agencies, have a role to play in the provision of DF-HTA. This, in turn, may improve the translation rate, ensuring that patients receive timely access to innovative engineering and technology solutions.

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