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Full title:

A toolkit of methods of development-focused health technology assessment

Running title:

Methods of development-focused HTA (35 characters)

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Abstract

Health technology assessment conducted to inform decisions during technology development (development-focused or DF-HTA) has a number of distinct features compared to HTA conducted to inform reimbursement and usage decisions. In particular, there are a broad range of decisions to be informed related to the development of a technology; multiple markets and decision-makers to be considered; a limited (and developing) evidence base; and, constrained resources for analysis. These features impact upon methods adopted by analysts. In this paper, we: 1) set out methods of DF-HTA against a timeline of technology development; 2) provide examples of the methods’ use; and 3) explain how they have been adapted as a result of the features of DF-HTA. We present a toolkit of methods for analysts working with developers of medical technologies. Three categories of methods are described: literature review, stakeholder consultation and decision analytic modelling. Literature review and stakeholder consultation are often used to fill evidence gaps. Decision analytic modelling is used to synthesise available evidence alongside plausible assumptions to inform developers about price or performance requirements. Methods increase in formality and complexity as the development and evidence base progresses and more resources are available for assessment. We hope this toolkit will be used in conjunction with the framework of features of DF-HTA presented in our earlier article in order to improve the clarity and appropriateness of methods of HTA used in DF-HTA. We also seek to contribute to a continuing dialogue about the nature of and best approach to DF-HTA.
**Key words**

Cost-effectiveness analysis, Technology assessment, Translational research, Research and development, early HTA

**Acknowledgements and Sources of Funding**

Janet Bouttell was funded by the Glasgow Molecular Pathology Node, an MRC ERSC funded project (MR/N005813/1). The other authors received no funding in relation to this work.

**Conflict of interest**

Andrew Briggs reports personal fees outside the submitted work from Takeda, Roche, GSK, Novartis, Merck, Bayer, Daiichi Sankyo and Astra Zeneca. Neil Hawkins reports personal fees outside the submitted work from Janssen-Cilag, Daiichi Sankyo, Bristol Myers Squibb, Bayer and Lilly. Janet Bouttell reports no conflict of interest.

**Introduction**

Health Technology Assessment (HTA) conducted to inform decision-making during the development of health technologies, which we term ‘development-focused HTA’ (DF-HTA), has a number of distinct features when compared to HTA conducted to inform reimbursement and usage decisions (‘use-focused HTA’). We have described these features in a previous article (1). These features may influence the selection of appropriate methods for DF-HTA.

Firstly, early in the development process, evidence specific to the technology being developed will be limited and rapidly evolving. Whereas, in use-focused HTA, evidence specific to the technology under consideration will be available and the evidence base will be comparatively better established. Secondly, DF-HTA may be used to inform a wide range of
decisions concerning whether or not to continue to invest in the development of a technology and the commissioning and design of further studies and analyses to support development and commercialisation. In turn, these decisions will require estimates of the acceptable price, expected revenues and comparative effectiveness for a technology, potentially across a range of candidate clinical contexts reflecting use in different positions in a clinical pathway (which themselves may vary across target markets) and technology design options. By way of contrast, use-focused HTA will be used to inform essentially binary decisions about whether or not a technology should be made available in a specific clinical context.

Thirdly, DF-HTA may need to consider the evaluation of technologies across multiple potential markets that have differing decision-making criteria and evidential requirements. For example, some markets may focus on estimates of cost-effectiveness obtained from decision analytic modelling whereas others may focus on assessments of comparative clinical value and pricing of comparable products. Use-focused HTA will typically focus on a specific market with well-defined evaluation criteria.

Finally, resources for HTA analysis will often be constrained. Small companies who do not yet have technologies on the market are likely to have limited funds available and larger companies will have multiple candidate technologies competing for available development funds. Proponents of DF-HTA will need to convince potential funders that DF-HTA activities will deliver a positive expected net return on the investment in these activities. There are basically two ways in which investment in DF-HTA activities can deliver a return - (a) by increasing expected revenue for a product by increasing the achieved price and/or by increasing sales volume or (b) by reducing development costs compared to what would have been achieved had the DF-HTA activities not taken place.
It should be noted that a return in terms of increased revenues can only be realised where the development is successful and a technology is commercialised. This is an important issue given the high rates of failure during early development. In principle, DF-HTA could increase expected returns on investment by helping to end development at an earlier stage for technologies that ultimately fail to generate revenue sufficient to cover their development costs. However, given that most technologies fail due to safety issues or lack of efficacy (2,3), it is unclear how effective DF-HTA will be at terminating development for high-risk candidates.

Developing medical technologies of all kinds is high risk, as investment costs are high and the chances of any individual technology in development reaching commercial success are relatively low (4). In pharmaceuticals, for example, it is estimated that forty percent of candidates entering clinical trial phases fail at phase one, sixty-four percent at phase two, thirty-eight percent at phase three and a further ten percent fail before approval (5). This means that just under twelve percent of pharmaceuticals entering clinical trials are eventually approved (5). Comparable data is not available for medical devices. In order to produce expected positive returns when used early in development, the costs of DF-HTA need to be commensurate with expected returns on the activity. This means that what might be regarded as best practice for use-focused HTA may not be appropriate in DF-HTA; DF-HTA is not simply HTA conducted earlier in development.

This article aims to set out broad groups of methods available to the DF-HTA analyst (who may be an academic, a consultant or an employee of the developer’s company), to provide examples of how and when the methods have been used and how they are adapted to the features of DF-HTA. We present a toolkit of methods for the DF-HTA analyst to use at
different stages of a research and development process. We hope it will be used in conjunction with the framework of features of DF-HTA presented in our earlier article (1) in order to improve the clarity and appropriateness of methods used in DF-HTA. We also seek to contribute to a dialogue about the nature of and best approach to undertaking DF-HTA.

We identified methods of DF-HTA from a review of published literature. The literature review used a pearl-growing approach (6) which aimed to identify examples of methods papers where the intended audience was developers of medical technologies. We used Ijzerman and Steuten’s (7) 2011 review article as the initial pearl. This approach involves reviewing the references and citations of the pearl for articles of interest, then reviewing the references and citations of the articles of interest until saturation is reached. The search was undertaken in October 2017 and refreshed in February 2019. From the initial review seven studies listed and described a selected group of methods (7-13). The Supplementary Materials include a table showing how the methods listed in previous review papers were categorised for the purposes of this paper (Supplementary Table 1) and provide definitions of methods of DF-HTA (Supplementary Table 2).

**Methods of development-focused HTA**

Table 1 shows three groups of methods useful in DF-HTA: literature review; stakeholder consultation and decision analytic modelling.

Table 1 – Toolkit of methods of DF-HTA

[Table 1 here]

DF-HTA – Development-focused Health Technology Assessment
The utility of each of the methods shown in Table 1 in DF-HTA depends upon the stage of development of the technology. Figure 1 shows an outline of a generic research and development process for a health technology. It is simplified in that it shows a simple linear process when, in reality, most research and development processes are more complex and involve elements of iteration. The figure also includes the purpose and methods of HTA which may be appropriate at each stage. In the first stage, DF-HTA is helping developers to articulate the value proposition for the technologies, at this stage there may be multiple value propositions. As the research and development of the technology progresses methods become more familiar to analysts undertaking HTA for reimbursement processes. The same methods are relevant at each stage, but the sophistication of the method increases as the development process extends when more resource for assessment may be available.

**Figure 1: Purpose and methods of health technology assessment at different stages of a research and development process**

[Figure 1 here]

**Stage 1 – basic research**

In this stage, DF-HTA activities can help developers to articulate the potential value propositions for the technology in development. By ‘value proposition’ we mean how the technology fulfils some need or want which potential customers may value. It is key at this stage to understand the current clinical pathways in jurisdictions of interest and how the technology may influence these pathways. Resources are likely to be restricted and methods of literature review, stakeholder consultation and decision analytic modelling need to be quick and simple.
Literature review is a key source of information in HTA. Published literature can provide information about prevalence and incidence in relevant populations, clinical pathways; current and potential comparators; and, estimates of costs and clinical effectiveness to populate decision analytic models. In the earliest stage of development, targeted literature reviews looking at only a small number of authoritative sources or even a single source may be appropriate (14-16). Clinical experts (and/or the developers) may be able to identify key sources such as relevant recent trials, guidelines or comprehensive HTA reports.

Both qualitative and quantitative methods of consulting clinical experts, patients or other stakeholders are widely used in DF-HTA. At the earliest stage of technology development only the most informal methods are likely to be feasible (interviews, for example) and the number of stakeholders and range of settings may be limited. Qualitative methods of stakeholder consultation encourage early interaction with stakeholders which can help to position the technology, articulate the value proposition/s and may lead to changes in direction of the development or design of the technology. A clear set of value propositions may help developers to raise finance and market their technology. Scenarios developed through stakeholder interaction may be useful to indicate where to focus effort in cost-effectiveness analysis. A technology needs to have the potential to add clinical value in terms of better health outcomes unless it is likely to be cheaper than the existing standard of care. Although it may be difficult to generalise results from consulting a small group of stakeholders from limited settings it should be remembered that at this stage we are focusing on the potential of the technology to add value. If it can do that in one place in the opinion of one set of stakeholders then that may be sufficient to justify continuation of the development.
Decision analytic modelling can be used at the earliest stages in development to estimate commercial pricing (‘headroom’) or a threshold for performance for the technology to be considered cost-effective in a given jurisdiction. This is useful for anticipating the maximum achievable price in jurisdictions where cost-effectiveness analysis based on an explicit threshold is a primary driver of reimbursement and usage decisions. Headroom is calculated by multiplying the increase in Quality Adjusted Life Years (or other relevant effectiveness metric) expected to be generated by the introduction of the new technology by an acceptable cost-effectiveness threshold then adjusting for cost savings/additional costs included in the calculation. The headroom estimate represents the maximum price achievable for the technology if it is to be considered cost-effective. (14,17) This price can be multiplied by expected volume of sales and costs of development deducted to provide an initial estimate of return on investment for the developer. The analysis may focus only on cost savings rather than valuing health outcomes (18) and may even be limited to the analysis of a single category of savings. (19)

**Example**

Kluytmans et al (2019) (20) undertook an ‘early assessment of proof of problem’ relating to a surgical instrument in development. The assessment comprised a stakeholder consultation and headroom calculation. The value proposition put forward by the developers was that the new flexible instrument could save time and reduce infections in meniscus surgery. The stakeholder consultation took the form of interviews with orthopaedic surgeons from two settings in the Netherlands. The surgeons considered that the maximum time saving which could be achieved was five minutes from a twenty-five-minute operation, which would probably not be enough to impact theatre schedules. They also noted that infection rates were already very low. Using the information from the stakeholder consultation, a headroom estimate was calculated. The estimate took an optimistic approach which assumed that the
technology delivered the full five-minute time saving and reduced infections to zero. A range of time savings and assumptions about price of the instrument were modelled to inform the developers. The conclusion of the analysis was that the instrument may need to be focused on an alternative indication as the estimated headroom was only €55.

**Stage 2 – translational research**
At this stage more resource may be available to extend the methods of DF-HTA beyond the quickest and simplest approaches described in Stage 1. Literature reviews may become more extensive and include a wider range of sources. Reviews are still likely to fall short of systematic reviews as even the briefest systematic review using automated tools has been estimated to require over 60-man hours (21) and a typical review takes over 800 man-hours estimate (22). The range of sources at this stage may include clinical guidelines, previous HTA reviews, online patient forums, regulatory reviews (such as European Public Assessment Reports), summaries of product characteristics and market analyses. Stakeholder consultation from the earliest stage of DF-HTA may have identified important sources of or requirement for information. For literature reviews during product development, Abel et al (2019) (23) recommend a ‘targeted’ approach where searches are conducted on a flexible, iterative basis and are interspersed with expert elicitation and stakeholder consultation.

Stakeholder consultation may also begin to use more formal methods and a wide range of both qualitative and quantitative methods are available. Relevant stakeholders will generally be potential users of the new technology (patients and clinicians) and/or decision-makers who may ultimately be involved in the purchase of the technology. Qualitative methods include interviews, focus groups, surveys, patient forums, online discussion groups and ‘Delphi’ panels. Delphi panels involve multiple rounds of consultations with experts with the aim of
reaching consensus. (24) Quantitative methods include multi-criteria decision analysis (MCDA), discrete choice experiments (DCE), and structured expert elicitation (SEE).

MCDA involves identifying a set of criteria for decision-making, determining the weight of each of the criteria, then scoring the alternatives against the identified criteria. (25) A simple points allocation approach is feasible where resources are limited. (25) A key issue in the use of MCDA in DF-HTA is the extent to which the MCDA exercise can formulate the questions and mimic the weights that actual decision-makers will use.

In DCE, respondents are asked to choose their preferred option amongst a set of options with differing attributes, one of which may be price. This reveals preferences and estimates of the relative importance of and willingness to trade between individual attributes associated with health care interventions or services. It differs from MCDA in that the ‘weights’ given to the individual attributes are revealed through the choices made rather than being explicitly elicited. Again, this could be used to model future decisions regarding the reimbursement or purchase of a new technology. In which case, the choices made should represent the preferences of the reimbursement agency or individual that will ultimately make the decision.

Structured Expert elicitation (SEE) uses quantitative methods of elicitation. Estimates may include probability distributions making them particularly suited to populate decision models for cost-effectiveness analysis. Online resources are available for SEE (26). Structured methods such as SEE, MCDA and DCE are likely to be beyond the budget of developers of health technologies in the early stages of development. Bojke et al, 2019 (27) recently undertook an expert elicitation exercise to validate a new framework and this took five months of researcher time. Indeed, even in the relatively well-resourced environment at
National Institute for Health and Care Excellence (NICE) expert elicitation is often done informally. (28) Our review identified a number of examples of the application of structured methods of stakeholder consultation, but studies have generally been undertaken in the context of a translational research body such as Center for Translational Molecular Medicine (CTMM). (29,30) Strengths of quantitative methods of stakeholder consultation include the explicit consideration of a range of relevant criteria which may inform developers in the design or required performance of the technology. The main limitation of these methods is the expertise and resource required to conduct them.

In the translational research stage decision analytic modelling can be used to explore a range of potential value propositions. For example, a technology may have potential in a number of places in the clinical pathway. A number of models could be produced to explore different levels of performance at different places in the clinical pathway. As there is generally little clinical evidence available and resources may still be constrained, modelling methods need to be simple. There may be a focus on cost-minimisation or cost-consequence analysis where this is seen as sufficient to inform decision-making by developers. Indeed, the development of a conceptual framework for a future cost-effectiveness analysis might be sufficient to identify evidential needs and to inform decisions regarding the commissioning and design of future studies. Other possible simplifications include shorter time horizons and the use of intermediate outcomes. This may avoid the need for sophisticated modelling but care needs to be taken to ensure that the consequences of these simplifications are understood.

Grutters et al (2019) (31) set out details of thirty-two assessments of technologies in development undertaken by their academic group in the Netherlands. In all thirty-two cases, the models developed were simple, deterministic models and sensitivity analysis undertaken was one-way rather than probabilistic. However, Annemans (32) has argued models constructed whilst technologies are in development should be the same level of complexity as
required to support an adoption decision at a later stage. It is argued that this is required so that the full complexity of the clinical and disease pathways is captured and all gaps in evidence identified. However, this approach may not be available to smaller developers where resources are constrained and may also be inefficient given that a large proportion of technologies in development do not reach commercial launch.(5)

It should also be noted that an iterative approach can be taken using a simple, deterministic model at first then developing a more complex model as required when specific clinical evidence becomes available. Initial low resource models may provide estimates which guide developers in positioning the technology and identify price and performance thresholds.

**Example**

Gc et al, 2021 (33) conducted an early HTA of wearable digital health technologies (WDHTs) to monitor chronic kidney disease (CKD) to support research and development decisions. As well as a literature review, the project included qualitative stakeholder consultation with patients and developers about what patients wanted and what this technology would be likely to add to existing provision. Economic evaluation was carried out in two stages; first, a simple initial evaluation identified key drivers of value for money then, following a discrete choice experiment which shed light onto patient preferences, a model-based cost-effectiveness analysis was undertaken incorporating headroom analysis, return on investment, one-way sensitivity and scenario analyses. The analysis showed that the novel WDHT had the potential to be cost-effective in the UK at a price up to £280.

**Stage 3 –clinical research**

As evidence specific to the technology starts to emerge, through the development process, more advanced methods of decision analytic modelling are appropriate. Stakeholder consultation becomes less relevant at this stage as the application of the technology has been
narrowed down and the most promising indication and position in pathway identified. As evidence of costs and clinical effectiveness becomes available, probabilistic analysis can be undertaken which quantifies the level of uncertainty. Value of information analysis, undertaken from the perspective of expected commercial returns for commercial sector developers, can be undertaken to illustrate where more evidence would be useful to reduce uncertainty. Such research may be worthwhile for the developer if reduced uncertainty increased the chances of the technology being adopted so increasing revenues beyond the cost of the evidence-generating activities. The evidence-base for health technologies other than pharmaceuticals may be under-developed as medical devices can be licenced in many jurisdictions with minimal levels of clinical evidence. There is a disincentive to produce evidence as ‘fast-followers’ may benefit without incurring cost if intellectual property protection is weak. In practice, resource constraint and the under-developed evidence base may restrict the use of VOI for DF-HTA. None of the 32 DF-HTA projects described by Grutters et al (31) involved VOI and Steuten et al, 2013 (34) found only three examples of VOI informing pre-market research and development. VOI conducted from a commercial perspective may be carried out more frequently but the extent of this is not clear. Budget impact analysis may be a useful extension of CEA undertaken using a decision analytic model, as budget impact forms part of reimbursement decision-making in some jurisdictions.

**Example**

Vallejo-Torres et al (2011), presented an iterative economic evaluation of absorbable pins for hallux valgus at three different stages of development (35). The authors used retrospective data for this analysis to recreate the dynamic process of DF-HTA occurring in real-time alongside the development process. At the earliest stage, the authors used observational data on standard methods and assumptions to estimate headroom for the absorbable pins. When
some data became available specific to the new technology, the authors built a decision model and presented one way sensitivity analysis. Only when evidence was available from a randomised controlled trial did the authors introduce additional complexity to their model in the form of probabilistic sensitivity analysis and value of information analysis.

Discussion

In this paper, we set out three broad groups of methods of DF-HTA: literature review; stakeholder consultation and decision analytic modelling. We explained how the use of these methods changes throughout the development of a technology and we provided examples. We also described how the methods were adapted to the particular features of DF-HTA. DF-HTA seeks to inform a broad range of decisions such as whether to continue to invest (go/ no go decisions), pricing strategy, optimum positioning in clinical pathways, technology design and evidence generation strategy. Methods need to be suited to answering this broad range so that DF-HTA has much greater focus on consultation with stakeholders than use-focused HTA. In particular, stakeholders can be useful to help position the technology at the earliest stages of development, to map out care pathways and provide estimates of parameter values in the absence of clinical evidence specific to the technology. Evidence from the literature is also of importance in DF-HTA but resource constraints mean that systematic reviews are seldom feasible and targeted reviews may need to be undertaken or expert guidance provided about the most authoritative sources to use. Informal methods of stakeholder consultation and simpler forms of decision analytic modelling (such as cost-minimisation or cost-consequence rather than cost-utility analysis, deterministic models and one-way sensitivity analysis) may be required when resources are constrained. These adaptations to methods may sit uncomfortably with experienced HTA analysts accustomed to the rigorous approaches required by publicly accountable reimbursement
bodies such as the National Institute for Health and Care Excellence (NICE) in the UK. (36) However, it should be remembered that in cases of resource constraint there may not be a choice between formal and adapted methods, just between adapted methods and no HTA input. (37) We would argue that developers have much to gain from the consideration of issues such as where the technology should be positioned, the articulation of its value proposition/s, initial cost-effectiveness analysis calculations and informal contact with stakeholders even at the earliest stages of development. The analyst must, of course, take care to ensure that the limitations of any adapted methods used are made clear to the developers at each stage of the analysis.

Current guidance on appropriate methods in the academic literature is limited. Commercial DF-HTA is often not published as there is no incentive to do so and the contents may be commercially sensitive. (31) There are bodies of work from projects such as Multidisciplinary Assessment of Technology Centre for Healthcare (MATCH UK) (14, 37-39) and the Center for Translational Molecular Medicine (CTMM) (7,18,40-41) which we have drawn on in this study. However, this published work may not be representative of DF-HTA, as within bodies such as MATCH and CTMM more resource may be available than is typically available for DF-HTA. Previous review articles have set out and described selected methods considered useful in the assessment of technologies in development (7-13). Markiewicz et al (2014) (11) set out to provide a comprehensive listing of methods of what the authors termed ‘Early HTA’. Stome et al (2019) set out analytical approaches useful in the early assessment of innovation in a healthcare setting. (42) This paper builds on these previous articles by grouping similar methods and removing methods which are not methods of assessment (such as bench studies and clinical trials which we would class as methods of research and development). Whilst we acknowledge that our categorisation of methods is
subjective, we believe that the simplification is justified as it makes the selection of methods of DF-HTA easier for the analyst. Recently Grutters et al (2019) (31) provoked a debate about the appropriate methods of health economic modelling. In this paper we make a further contribution to that debate.

There are several limitations to our work. The most important limitation is that little DF-HTA is published due to commercial sensitivities and lack of incentive to publish (43). Our literature review may not have retrieved all relevant articles and both our inclusion criteria and categorisation were necessarily subjective. However, we hope that this toolkit of methods, together with our framework of features previously described (1), will provide an introduction to the particular requirements of HTA conducted to inform developers. For the wider academic community, we hope to add to the debate about what are appropriate methods of HTA to inform developers. Further research which would be of use includes studies examining the methods used in DF-HTA in the commercial context.

References


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<thead>
<tr>
<th>Analytic methods (Sub-types)</th>
<th>What the method involves</th>
<th>Information provided</th>
<th>Adaptations to the method for the purposes of DF-HTA</th>
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| Literature review | Review of publicly available information and the academic literature | Existing care pathways  
Evidence of clinical effectiveness for technology and comparator  
Evidence of costs and utilities for comparator and potentially for technology  
Identification of current and potential comparators  
Barriers and facilitators for diffusion to inform economic model structure and/or scenarios for analysis. | Less rigorous methods than systematic review.  
Reliance on small range of authoritative sources such as guidelines/HTA reports/summaries of product characteristics at earliest stages. |
| Stakeholder consultation | Consulting clinical experts, patients or other stakeholders. Delphi panels involve two rounds of consultation to achieve a consensus | Articulation of value propositions  
Evidence of clinical effectiveness for technology and comparator  
Insight into contextual aspects requiring consideration in design.  
Barriers and facilitators for diffusion to inform economic model structure and/or scenarios for analysis. | Less formal methods used  
Smaller numbers consulted  
Limited number of settings |
| Qualitative methods including:  
• Interviews  
• focus groups  
• surveys  
• patient forums  
• online discussion groups  
• Delphi panels | Methods use different means to structure the consultation. MCDA compares alternatives using weighted criteria. DCE uses pairwise comparisons to reveal preferences for attributes. SEE uses quantitative methods to derive point estimates and ranges or distributions for parameters | Evidence of clinical effectiveness for technology and comparator  
Estimates of costs and utilities for comparator and potentially for technology  
Evidence to support pricing strategies  
Preferences of decision makers/users for attributes of a new technology | Less complex methods such as those based on points allocation for MCDA.  
Smaller numbers of stakeholders consulted. Limited range of settings |
| Quantitative methods including:  
• Multi-criteria decision analysis (MCDA)  
• Discrete choice experiments (DCE)  
• Structured expert elicitation (SEE) | Comparing the costs and health outcomes of existing and potential care pathway. Estimating the value of further research to society or a decision maker | Commercial headroom  
Target thresholds for development costs, pricing and clinical effectiveness/test performance  
Evidence gaps | Simple models  
Multiple scenarios  
Shorter time horizons  
Intermediate outcomes |
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<tr>
<td>cost benefit analysis&lt;br&gt;cost minimisation analysis&lt;br&gt;estimation of headroom, budget impact analysis)</td>
<td>commercial developer using a probabilistic decision analytic model</td>
<td>Reimbursement potential&lt;br&gt;Potential cost savings&lt;br&gt;Budget impact&lt;br&gt;Estimates of the societal or commercial value of further research&lt;br&gt;Identification of influential parameters for reducing uncertainty in cost-effectiveness&lt;br&gt;Estimate of optimum sample sizes</td>
<td>Use of cost minimisation and cost consequence analysis&lt;br&gt;One-way sensitivity analysis&lt;br&gt;Too complex for use in DF-HTA unless well resourced.</td>
</tr>
<tr>
<td>Value of information analysis&lt;br&gt;(Expected value of perfect information, expected value of partial parameter information, expected value of sampling information)</td>
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