Guidance on the integrated assessment of complex health technologies –

The INTEGRATE-HTA Model

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INTEGRATE-HTA

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PROJECT:

Integrated Health Technology Assessment for Evaluating Complex Technologies (INTEGRATE-HTA)

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About this guidance

Who would find this guidance useful?

This guidance is useful for agencies, organizations, and institutions that compile and use health technology assessment (HTA) reports.

Purpose and scope of this guidance

The purpose of this guidance is to provide methods for an integrated assessment of complex health technologies. It describes a systematic process (the INTEGRATE-HTA Model) for assessing complex technologies that involves stakeholders, considers effectiveness, cost-effectiveness, ethical, socio-cultural and legal aspects, patient characteristics, as well as context and implementation issues. The INTEGRATE-HTA Model outlines an integrated scoping process, a coordinated application of assessment methods for different aspects and an integrated and structured decision-making process. It is based on concepts and methods presented in the other methodological guidances developed in the INTEGRATE-HTA project (www.integrate-hta.eu).

Added value for an integrated assessment of complex technologies

Traditional HTA assesses technologies independent of context, implementation issues, and patient characteristics. It also assesses different aspects of a technology only side-by-side and not in an integrated way. The INTEGRATE-HTA Model presented in this guidance structures assessments of complex technologies which take context, implementation issues, and patient characteristics into account and might thus be more meaningful for real-life decision-making.

INTEGRATE-HTA

INTEGRATE-HTA is an innovative project that was co-funded by the European Union under the Seventh Framework Programme from 2013 till 2015. Using palliative care as a case study, this project developed concepts and methods that enable a patient-centred, comprehensive, and integrated assessment of complex health technologies.

Guidance on the integrated assessment of complex health technologies - The INTEGRATE-HTA Model

Executive Summary

Challenges in assessments of health technologies

In recent years there have been major advances in the development of health technology assessment (HTA). However, HTA still has certain limitations when assessing technologies which

- are complex, i.e. consist of several interacting components, target different groups or organizational levels, have multiple and variable outcomes, and/or permit a certain degree of flexibility or tailoring (Craig et al., 2008),
- are context-dependent - current HTA usually focusses on the technology, not on the system within which it is used,
- perform differently depending on the way they are implemented,
- have different effects on different individuals.

Furthermore, HTA usually assesses and appraises aspects side-by-side, while decision-making needs an integrated perspective on the value of a technology. In the EU-funded INTEGRATE-HTA project, we developed concepts and methods to deal with these challenges, which are described in six guidances.

Because of the interactions, an integrated assessment needs to start from the beginning of the assessment. This guidance provides a systematic five-step-process for an integrated assessment of complex technologies (the INTEGRATE-HTA Model).

Purpose and scope of the guidance

The aim of the INTEGRATE-HTA project is to provide concepts and methods that enable a patient-centred, comprehensive, and integrated assessment of complex health technologies. The purpose of this guidance is to structure the overall HTA-process. The INTEGRATE-HTA Model outlines an integrated scoping process, a coordinated application of assessment methods for different aspects and an integrated and structured decision-making process. It is intended for HTA agencies, HTA researchers and those engaged in the evaluation of complex health technologies. As it links the assessment to the decision-making process, it also addresses HTA commissioners and other stakeholders using or planning HTAs.

While all technologies are arguably complex, some are more complex than others. Applying this guidance might lead to a more thorough and therefore more time-consuming process. Depending on the degree of complexity, one might choose to follow the whole process as described in this guidance, or only focus on certain steps. The guidance provides an operational definition to assess the complexity of technologies which can be used to identify specific aspects that will need more attention than others. What the guidance does not provide is a post-hoc solution for assessments that have already been completed.

Development of the guidance

The INTEGRATE-HTA Model presented in this guidance was developed based on a systematic literature search on approaches for integration, on the experiences of traditional HTAs, as well as on the other methodological guidances developed in the INTEGRATE-HTA project. It was tested in a case study on palliative care and iteratively revised during the practical application. The guidance was again revised after internal and external peer-review.

Application of this guidance

For a comprehensive integrated assessment of a complex technology, we developed a five-step process, the INTEGRATE-HTA model. In Step 1, the HTA objective and the technology are defined with the support from a panel of stakeholders. An initial logic model is developed in Step 2. The initial logic model provides a structured overview of the technology, the context, implementation issues, and relevant patient groups. It then frames the assessment of the effectiveness, as well as economic, ethical, legal, and socio-cultural aspects in Step 3. In Step 4, a graphical overview of the assessment results, structured by the logic model, is provided. Step 5 is a structured decision-making process informed by the HTA (and is thus not formally part of the HTA, but follows it).

- **Step 1:** In step 1, the technology under assessment and the objective of the HTA are defined. Especially for complex technologies, such as palliative care, the definition of the technology alone is a challenge that must not be underestimated. It is recommended to do this based on a tentative literature review and with the support of stakeholder advisory panels (SAPs) which should comprise clinical experts, academics, patients, possibly their relatives and/or other caretakers, and the public. The setting of an objective considering all relevant aspects of complexity and structured by assessment criteria is important. The assessment criteria will usually reflect values of the stakeholders as well as the input from the theoretical, methodological and empirical literature.

- **Step 2:** In step 2, an initial logic model is developed (see Guidance on the use of logic models in health technology assessments of complex interventions). The model provides a structured overview on participants, interventions, comparators, and outcomes. Parallel to this, groups of patients that are distinguished by different preferences and treatment moderators (see Guidance for the assessment of treatment moderation and patients' preferences) are identified. Specific context and implementation issues are also identified as part of the initial logic model (see Guidance for the Assessment of Context and Implementation in Health Technology Assessments (HTA) and Systematic Reviews of Complex Interventions). The product of this step is the logic model as a graphical representation of all aspects and their interactions that are relevant for the assessment of the complex technology.

- **Step 3:** In step 3, the logic model serves as a conceptual framework that guides the evidence assessment. Depending on the specific aspect (e.g. effectiveness, economic, ethical, socio-cultural, or legal aspects) different methods are available for the assessment (see Guidance for assessing effectiveness, economic aspects, ethical aspects, socio-cultural aspects and legal aspects in complex technologies). The outputs of step 3 are evidence reports and standardized evidence summaries for each assessment aspect (e.g. report on economics, report on ethical aspects, etc.).

- **Step 4:** In step 4, the assessment results of step 3 are structured using the logic model developed in step 2. Whereas the initial logic model in step 2 specifies what evidence is relevant, the extended logic model to assist decision-making in step 4 visualizes the assessment results as well as the interaction with respect to the HTA objectives. It also allows for the consideration of different scenarios depending on the variation in context, implementation and patient characteristics.

- **Step 5:** Step 5 involves a structured decision-making process and is not an integral part of the HTA in the narrow sense. Decision-making can be supported by applying quantitative e.g. MCDA- (Multi-criteria decision analysis) or qualitative decision support tools. Flexibility in the application of these tools by the decision committee is crucial, taking different decision settings and evidence needs into consideration.

Conclusions

In current HTA, different aspects are usually assessed and presented independent of each other. Context, implementation issues and patient characteristics are rarely considered. The INTEGRATE-HTA Model enables a coordinated assessment of all these aspects and addresses their interdependencies. The perspective of stakeholders such as patients and professionals with their values and preferences is integrated in the INTEGRATE-HTA Model to obtain HTA results that are meaningful for all relevant stakeholders. Finally, health policy makers obtain an integrated perspective of the assessment results to achieve fair and legitimate conclusions at the end of the HTA process. The application of the model will usually require more time and resources than traditional HTA. An initial assessment of the degree and the character of complexity of a technology might be helpful to decide whether or not the whole process or only specific elements will be applied.

Guidance on the integrated assessment of complex health technologies - The INTEGRATE-HTA Model

List of abbreviations

AHP	Analytic Hierarchy Process
ANP	Analytic Network Process
BN	Bayesian Network
BWS	Best-Worst Rating
CADTH	Canadian Agency for Drugs and Technologies in Health
CICI	Context and Implementation for Complex Interventions
COPE	Creativity, Optimism, Planning, and Expert Information
CRP	Consensus Reaching Process
DCE	Discrete Choice Experiment
DST	Dempster–Shafer Theory
ELECTRE	ELimination and Choice Expressing REality
EUnetHTA	European network for Health Technology Assessment
EVPI	Expected Value of Perfect Information
EVPPI	Expected Value of Partial Perfect Information
EVIDEM	EVIdence based DEcision Making
G-BA	Gemeinsamer Bundesausschuss
GRADE	Grading of Recommendations Assessment, Development and Evaluation
INTEGRATE-HTA	Integrated Health Technologies Assessment for the Evaluation of Complex Technologies
INAHTA	The International Network of Agencies for Health Technology Assessment
IQWiG	Institute for Quality and Efficiency in Health Care
HTA	Health Technology Assessment
MACBETH	Measuring Attractiveness by a Category Based Evaluation Technique
MAUT	Multi-Attribute Utility Theory
MCDA	Multi-criteria Decision Analysis
MRC	Medical Research Council
NGT	Nominal group technique
NICE	National Institute for Health and Care Excellence
NIS	Negative Ideal Solution
PBMA	Programme Budgeting and Marginal Analysis
PIS	Positive Ideal Solution
PROMETHEE	Preference Ranking Organisation Method for Enrichment Evaluation
REMBRANDT	Ratio Estimation in Magnitudes or deci-Bells to Rate Alternatives which are Non-DominaTed
SAP	Stakeholder Advisory Panel
SEU	Subjective Expected Utility
SMARTS	Simple Multi-Attribute Rating Technique Using Swings
TOPSIS	Technique for Order Preference by Similarity to Ideal Solution
VOI	Value of Information

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1 PURPOSE AND SCOPE OF THE GUIDANCE

1.1 AIM OF THIS GUIDANCE

The aim of the INTEGRATE-HTA project is to provide concepts and methods that enable a patient-centered, comprehensive, and integrated assessment of complex health technologies. The Oxford English dictionary defines integration as "…the making up or composition of a whole by adding together or combining the separate parts or elements; combination into an integral whole" (Stevenson, 2005). Following the definition of the Oxford dictionary, this guidance focuses on how to achieve an integrated assessment process of aspects relevant for complex technologies from the outset of the assessment to the final decision (the INTEGRATE-HTA Model).

1.2 TARGET AUDIENCE FOR THIS GUIDANCE

This guidance is intended for HTA agencies, HTA researchers and those engaged in the evaluation of multiple aspects of complex health technologies. It is also useful for HTA commissioners and other stakeholders using or planning to do HTAs. This guidance supports health policy makers in making deliberative decisions by facilitating a transparent and comprehensive HTA process.

1.3 THE ADDED VALUE OF THIS GUIDANCE IN RELATION TO EXISTING GUIDANCE

The focus of this guidance is on the integration of aspects relevant for the assessment of complex technologies. Three guidances were useful as starting points for this guidance:

The Core Model of the 'European network for health technology assessment' (EUNetHTA) (Lampe et al., 2009), which provides a comprehensive framework for various aspects of health technology assessments;

The British Medical Research Council (MRC) developed a framework that specifically focuses on the development and evaluation of complex interventions (Craig et al., 2008; Moore et al., 2015).

The Canadian Agency for Drugs and Technologies in Health (CADTH), which provides guidelines on health economic evaluations, taking various aspects such as preferences for outcomes, equity, generalizability, uncertainty and variability into account (CADTH, 2006).

However, all these guidances only provide an account of methods that can be used concurrently, for each of the assessment aspects; they do not address how to integrate the different assessment results.

The "Guidance for the methods of technology appraisal 2013" from the National Institute for Health and Care Excellence (NICE) divides the HTA process into scoping, assessment and appraisal. The fiinal appraisal takes the uncertainty of the HTA results, the transferability of the results to the decision context, and implementation issues into account when interpreting the evidence (NICE, 2013). In addition to the NICE approach, we provide an integrated HTA process (the INTEGRATE-HTA Model; for details see chapter 3) that structures the assessment of different aspects. We also consider aspects that are specifically relevant for the assessement of complex technologies such as context and implementation issues.

The instrument GRADE (Grading of Recommendations Assessment, Development and Evaluation) aims to assess the quality of evidence, the balance of desirable and undesirable consequences, values and preferences, and the use of resources. The INTEGRATE-HTA Model acknowledges the parts of the GRADE assessment that are formal and rigorous (such as on quality of evidence). Our approach adds a systematic process for the parts of GRADE that are not formalized (such as assessment of values and preferences). As GRADE does not inform users about how to take qualitative evidence such as context and implementation issues into account, it was developed further resulting in the instrument DECIDE (Developing and Evaluating Communication Strategies to Support Informed Decisions and Practice Based on Evidence) (Guldbrandsson et al., 2015). DECIDE extends the list of criteria that are provided by GRADE and provides computer-based tools to comprehensively illustrate different criteria and the underlying evidence. All the same, these criteria are presented alongside one another rather than in an integrated manner. The INTEGRATE-HTA Model provides a process and tools to integrate all assessment criteria.

The methodological approach of Multi-criteria Decision Analysis (MCDA) is a well-known tool to address the challenges of integrating dimensions of information. Belton described MCDA as "an umbrella term to describe a collection of formal approaches which seek to take explicit account of multiple criteria in helping individuals or groups explore decisions that matter" (Belton & Stewart, 2002). MCDA has been used as a basis for developing evaluation tools such as the EVIDEM (EVIdence based DEcision Making) framework, which specifically adapted MCDA for HTA decision-making.

Accordingly, this guidance also builds on the work of the EVIDEM framework. The framework consists of 15 quantifiable core criteria that are specific for HTA decision-making, such as severity of disease. The 15 core criteria are weighted independently from the assessed technology. The performance of the technology is then scored against each core criterion and a value estimate is calculated by combining weights and scores. Finally, qualitative considerations can be taken into account for final decision-making (Goetghebeur et al., 2008). The EVIDEM framework was widely tested in different decision settings for HTA (Goetghebeur et al., 2012; Goetghebeur et al., 2010; Miot et al., 2012; Tony et al., 2011; Wahlster et al., 2015b). EVIDEM, however, does not cover all relevant aspects for the assessment of complex technologies, e.g. patient characteristics, context and implementation issues. Even though many criteria such as "System capacity" and "Unmet needs" are interrelated, the assessments of different criteria are not linked to each other. The INTEGRATE-HTA Model addresses these interdependencies from the very beginning and considers the work of EVIDEM in step 5 of the INTEGRATE-HTA Model.

1.4 LOCATING THE GUIDANCE IN THE INTEGRATE-HTA PROJECT

This guidance builds on all other methodological guidances developed in the INTEGRATE-HTA project:

- Guidance on the use of logic models in health technology assessments of complex interventions,
- Guidance for the Assessment of Context and Implementation in Health Technology Assessments (HTA) and Systematic Reviews of Complex Interventions: The Context and Implementation of Complex Interventions (CICI) Framework,
- Guidance for the assessment of treatment moderation and patients' preferences,
- Guidance for assessing effectiveness, economic aspects, ethical aspects, socio-cultural aspects and legal aspects in complex technologies,
- Guidance on choosing qualitative evidence synthesis methods for use in health technology assessments of complex interventions.

The guidance presented here structures the application of the other methodological guidances into a five-step systematic assessment process (the INTEGRATE-HTA Model).

The "Guidance on the use of logic models in health technology assessments of complex interventions" (Rohwer et al., 2016) is applied to develop the scope of the HTA. Logic models provide an overview of the current knowledge about complex technologies. A logic model is "... a graphic description of a system ... designed to identify important elements and relationships within that system" (Anderson et al., 2011; Kellog, 2004). Based on the HTA objective (see chapter 3.1), an initial logic model that provides an overview of the current conditions regarding the technology under investigation is drafted in step 2 (see chapter 3.2).

Relevant aspects regarding patient preferences and context and implementation issues are identified by applying the "Guidance for the assessment of treatment moderation and patients' preferences" (Van Hoorn et al., 2016) and the "Guidance for the Assessment of Context and Implementation in Health Technology Assessments and Systematic Reviews of Complex Interventions: The Context and Implementation of Complex Interventions (CICI) Framework" (Pfadenhauer et al., 2016), and feed into the initial logic model to inform the evidence collection in step 2 (see chapter 3.2).

For the evidence assessment, the "Guidance for assessing effectiveness, economic aspects, ethical aspects, socio-cultural aspects and legal aspects in complex technologies" (Lysdahl et al., 2016) is applied in step 3 (see chapter 3.3).

The "Guidance on choosing qualitative evidence synthesis methods for use in health technology assessments of complex interventions" (Booth et al., 2016) supports the synthesis of evidence depending upon the type of data being synthesised at multiple points of the INTEGRATE-HTA Model.

2 BACKGROUND

2.1 HTA OF COMPLEX TECHNOLOGIES

The UK Medical Research Council (MRC) defines complex interventions as being characterised by the number of interacting components within the experimental and control interventions, the number and difficulty of behaviours required by those delivering or receiving the intervention, the number of groups or organisational levels targeted by the intervention, the number and variability of outcomes, and the degree of flexibility or tailoring of the intervention permitted eigentlich (Craig et al.,2008). Shiell (Shiell et al., 2008) highlight that complexity is a characteristic of the system within which an intervention acts as well as being an inherent characteristic of an intervention itself. They describe complex systems as being adaptive to their local environment, as behaving non-linearly and as being part of hierarchies of other complex systems.

Many of the traditional methods of analysis in HTA rely upon specific assumptions about the structure, content and objectives of an intervention, its implementation, the system within which it is intended to act and the potential interplay and co-evolution of the system and the intervention. However, to avoid misleading conclusions, HTA should take the complexity of a technology and/or the complexity of its environment into account.

For example, when assessing a technology such as an educational program to prevent the transmission of the human immunodeficiency virus (HIV) the success or failure might depend on the message itself (e.g. abstention or condoms or both), the messenger (a young celebrity or a respected religious leader), the target group (sexually active adolescents or elderly religious persons), the medium transmitting the message (internet spots or lectures), the perceived prevalence of the disease (omnipresent threat or small chance), and so on. Simply to focus on the content of the program without considering these other factors is not sufficient.

Complexity is not a binary property, and exists rather along a spectrum. All interventions could, therefore, be considered complex to a certain extent. This guidance, however, focuses on those health technologies where the presence of complexity has strong implications for the planning, conduct and interpretation of the HTA. Table 1 lists potentially relevant characteristics of complexity.

Consequently, when starting an assessment of (any) health technology these factors should be carefully reviewed with the purpose of

1. describing the complexity of an intervention and the system within which it acts,
2. understanding whether this complexity matters for decision making and therefore needs to be addressed in an HTA,
3. understanding the implications of complexity for the methods of HTA analysis in assessing the ethical,

Table 1: Synthesis of potentially relevant characteristics of complexity in HTA.

Characteristic	Short explanation
1 Multiple and changing perspectives	The variety of perspectives is caused by the many components (social, material, theoretical, and procedural), actors, stakeholders, organizational levels that are involved in the intervention. These are in addition interconnected and interacting, and accordingly exposed to changes.
2 Indeterminate phenomena	The interventions or condition cannot be strictly defined or delimited due to characteristics such as flexibility, tailoring, self-organization, adaptivity and evolution over time.
3 Uncertain causality	Factors such as synergy between components, feedback loops, moderators and mediators of effect, context, symbolic value of the intervention, lead to uncertain causal pathways between intervention and outcome.
4 Unpredictable outcomes	The outcomes of the intervention may be many, variable, new, emerging and unexpected.
5 Historicity, time and path dependence	Complex systems evolve through series of irreversible and unpredictable events. The time, place and context of an intervention therefore impact on the effect, generalizability and repeatability of an intervention.

legal, effectiveness, economic and socio-cultural aspects of an intervention, and

4. exposing important factors that decision makers need to consider in interpreting the HTA.

2.2 WHICH DIMENSIONS OF INFORMATION NEED TO BE INTEGRATED IN HTA?

Different dimensions of information need to be integrated in HTA. These are:

1. Different assessment aspects of a health technology, such as legal or economic aspects,
2. Modifying factors, such as patient characteristics, context and implementation issues
3. Uncertainty of the assessment results, such as validity of evidence
4. Representation of stakeholders with their values and preferences

These dimensions were continuously taken into account during the development process of the INTEGRATE-HTA Model and are described in detail in this chapter.

2.2.1 Dimension 1: Different assessment aspects of a health technology

The assessment aspects (dimension 1) comprise effectiveness, socio-cultural, economic, ethical and legal issues. Each aspect (i.e. effectiveness, legal issues) is assessed by a specific assessment method. The result is a separate evidence report for each assessment aspect. Figure 1 illustrates the different assessment aspects of an HTA report. The second dimension of information that needs to be integrated, compromises factors that can modify the assessment results (dimension 1).

2.2.2 Dimension 2: Modifying factors: context, implementation issues and patient characteristics

This dimension includes context, implementation issues and patient characteristics. When assessing the different assessment aspects (dimension 1), the influence of patient characteristics, implementation issues and context (dimension 2) has to be considered (see figure 2).

Context is defined as "a set of characteristics and circumstances that surround the implementation effort." Implementation is conceptualized as "a planned and deliberately initiated effort with the intention to put an intervention into practice" (see "Guidance for the Assessment of Context and Implementation in Health Technology Assessments (HTA) and Systematic Reviews of Complex Interventions: The Context and Implementation of Complex Interventions (CICI) Framework") (Pfadenhauer et al., 2016).

Patient characteristics can be separated into patient moderators and patient preferences (see the "Guidance for the assessment of treatment moderation and patients' preferences") (Van Hoorn et al., 2016). Patients with a particular disease or condition may respond quite differently to the same treatment (patient moderator). Additionally, patients may not appreciate all treatment outcomes in the same way (patient preferences). For example, they may differ within their values regarding pain and duration of life. Relieving pain through opioids can worsen symptoms such as fatigue or nausea.

Figure 1: Different assessment aspects of a health technology produce different assessment results that need integration.

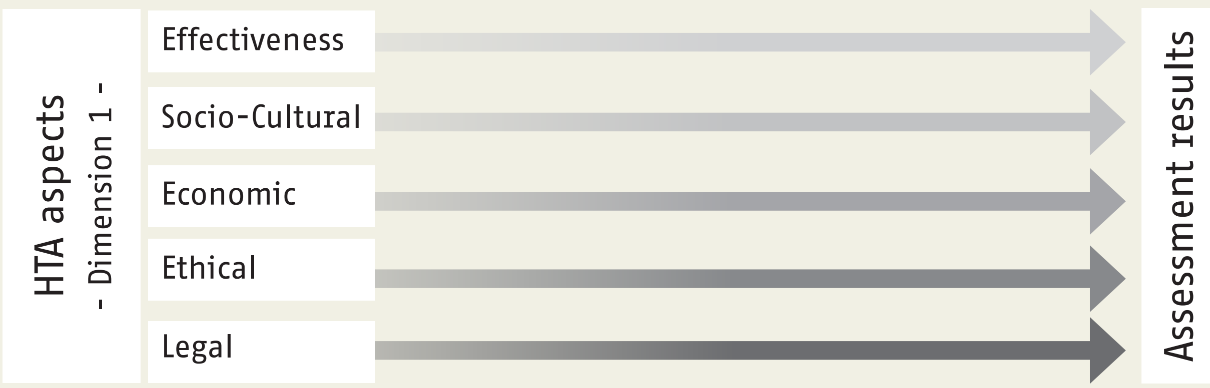
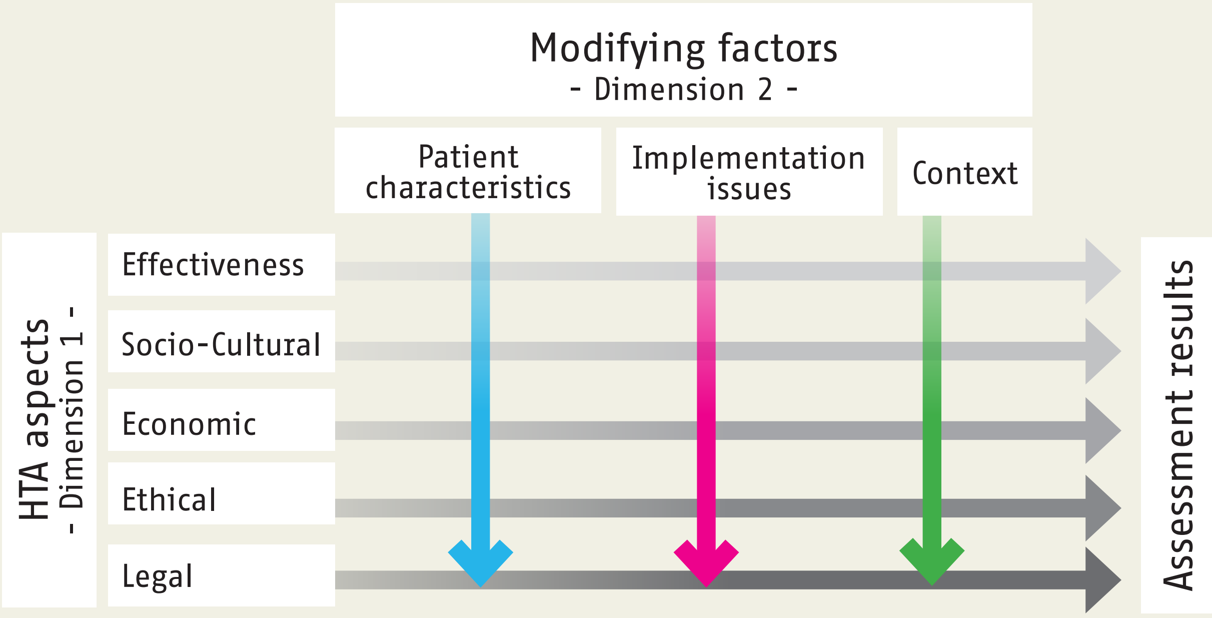


Figure 2: Impact of modulating factors on outcomes.



The resulting "trade-offs" between different outcomes will vary between different patients according to their preferences

Modifying factors (dimension 2) need to be described and considered carefully (e.g. contextual factors that affect the transferability of study results from another health care system) as they play an important role in the estimation of uncertainty of the assessment result (dimension 3).

2.2.3 Dimension 3: Uncertainty of the assessment results

Any assessment result (from dimension 1) needs to be reported together with its degree of uncertainty (dimension 3), e.g. the likelihood of obtaining a certain outcome such as pain relief. Uncertainty is related to the internal validity (such as the choice of indicators, risk of bias), and also to the transferability of the evidence to the specific situation under assessment.

2.2.4 Dimension 4: Representation of stakeholders, including their values and preferences

The perspectives of stakeholders (such as patients, physicians and decision makers), including their values and preferences, represent the fourth dimension of information in HTA. Stakeholders should be part and parcel of HTA, and should be included in a structured, transparent and fair manner. Accordingly, the values and preferences of the stakeholders interact with all other dimensions. They influence the aspects and outcome parameters to assess (dimension 1), identify and interpret the influence of the modifying factors (dimension 2), and decide on the acceptability and interpretation of uncertainty regarding the assessment results (dimension 3).

3 DEVELOPMENT OF THE INTEGRATE-HTA MODEL

3.1 IMPLICATIONS REGARDING THE DIMENSIONS OF INFORMATION IN HTA FOR THE DEVELOPMENT OF THE INTEGRATE-HTA MODEL

As comprehensive strategies for an integrated assessment of all dimensions of information in HTA are missing, we developed a new approach, the INTEGRATE-HTA Model. The development of the INTEGRATE-HTA Model is based on the assumption that the aspects to be assessed (dimensions 1 such

Figure 3: Impact of uncertainty on the assessment results.

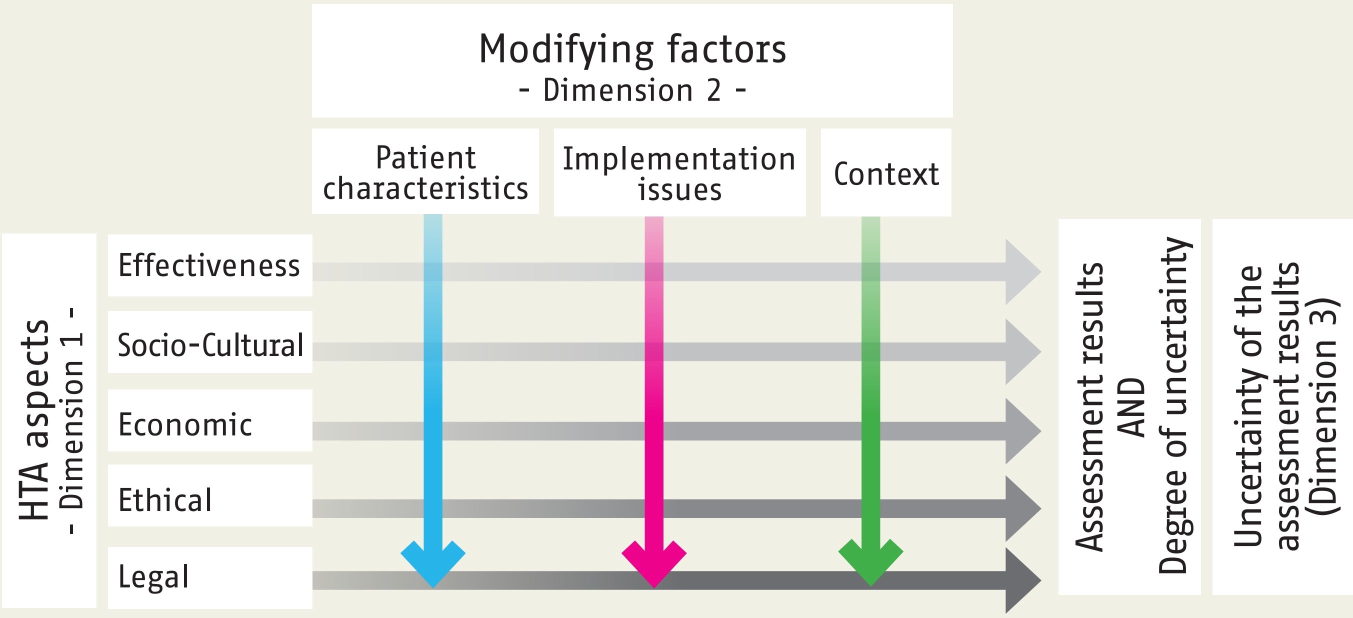
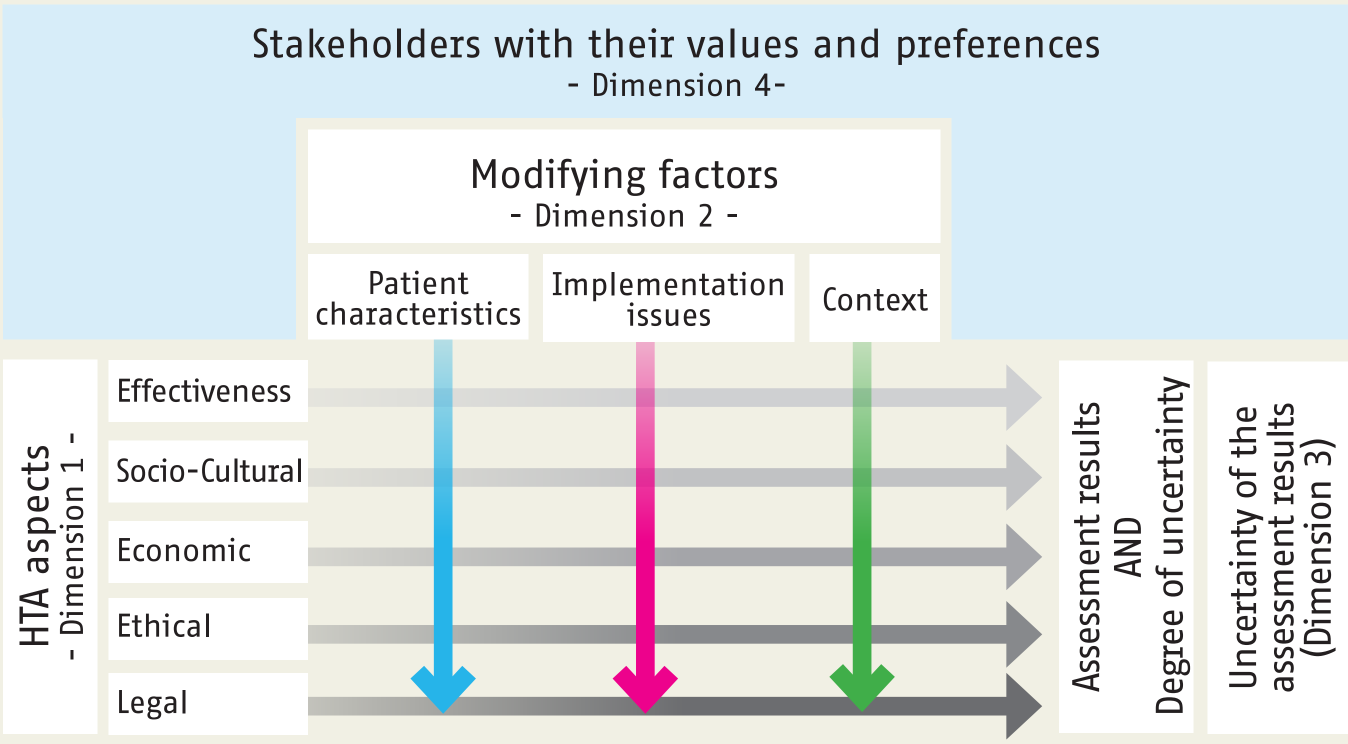


Figure 4: Impact of stakeholders and their values and preferences.



as effectiveness, ethical or socio-cultural aspects) strongly interact with each other, with context and implementation issues and patient characteristics (dimension 2), the degree of uncertainty (dimension 3), and stakeholder values and preferences (dimension 4).

This has four implications:

1. The aspects of (complex) technologies (dimension 1) cannot be assessed independent of context, implementation issues, and patient characteristics (dimension 2). These need to be identified and their interactions need to be taken into account.
2. Integration between the different dimensions is a continuous process. It is not possible to assess the different, interacting dimensions independently first, and complete the integration afterwards.
3. The resulting number of combinations regarding the diversity of modifying factors (e.g. patient preferences for outcome a, b, c multiplied with different contextual scenarios x, y, z) is virtually infinite. Therefore, explicit choices regarding the assessment aspects (dimension 1) and modifying factors (dimension 2) need to be made at the beginning of the assessment.
4. Stakeholders (such as patients, physicians or decision makers) have different information needs: While some specifically want to understand interactions and uncertainties of complex technologies, others prefer a more condensed version of results.

As the different dimensions to be integrated require different methods for integration, we conducted a mapping review of the medical and non-medical literature to identify methods to integrate the different dimensions of information in HTA.

3.2 MAPPING REVIEW OF METHODS TO INTEGRATE THE DIFFERENT DIMENSIONS OF INFORMATION IN HTA

A systematic literature search was performed to identify articles on integration methods published in medical and non-medical databases between January 2004 and April 2014. Databases and keyword terms are provided in the appendix (see chapter 8.1.1).

Integration methods were defined as existing methodologies for integrating different dimensions of information. These methods were appraised for applicability to HTA. They were included if they were deemed to be useful to integrate at least two of the four dimensions of information. Detailed inclusion criteria are listed in the appendix.

The four dimensions of information in HTA were used as categories for data extraction (table in appendix).

30 methods for integration were included in the mapping review. We divided these methods into four groups: MCDA methods, preference elicitation methods, analytic methods and consensus methods.

MCDA methods mainly consist of four different steps.

- Criteria are developed for the assessment of the technology, such as public health impact, as separate criterion.
- Weights for each criterion are derived, representing the relative importance given by stakeholders to each criterion.
- The performance of a technology against each criterion is assessed and scored.
- Based on the weights and the scores for the performance, an integrated measure is calculated. MCDA can thus provide insights into decision-making processes in terms of preferences and values of decision makers, and the alternatives to decide on.

The common features of preference elicitation methods are the separation of a decision into different decision criteria corresponding to MCDA methods. Afterwards, these criteria form the basis for the creation of hypothetical decision options with different criteria values. Decision makers need to decide between these options according to their preferences. These choices are translated into quantitative preference scores for the different decision criteria and decision options. Finally, the decision options can be ranked according to these preference scores.

An aspect of analytic methods is the definition of a decision problem. A decision problem might be whether a new health technology can significantly improve the health of a specific population. Accordingly, different sources of evidence that are related to the decision problem are identified, such as population data and a clinical trial about the new technology. The relationship between these different pieces of evidence is modelled, and quantitative calculations of these relationships are performed. Finally, integrated data are obtained as results of these calculations and used to support decision-making. Thus, analytic methods provide insights into the likelihood and the magnitude of an effect of new health technologies.

Consensus methods describe methods for a structured discussion and decision-making. The objective is to achieve consensus among participants through applying these methods. General consensus methods are used for discussions of the final information (in this case the assessment results of the HTA) that informs the decision. Process-based consensus methods are used for discussions during the assessment process that results in the final information for decision-making.

A description of each method is provided in chapter 8.1.2 (in the appendix). As a method can consist of several integration techiques the methods were disaggregated into the underlying techniques. The methods were disaggregated into different techniques. Techniques were defined as similar patterns of integration in different methods. Nine techniques that cover specific dimensions of information in HTA (chapter 1.2.1) were subsequently identified. A detailed description of each technique is provided in chapter 8.1.3 in the appendix. The INTEGRATE-HTA Model that is presented in the following chapter was developed based on these methods and techniques.

4 APPLICATION OF THE GUIDANCE

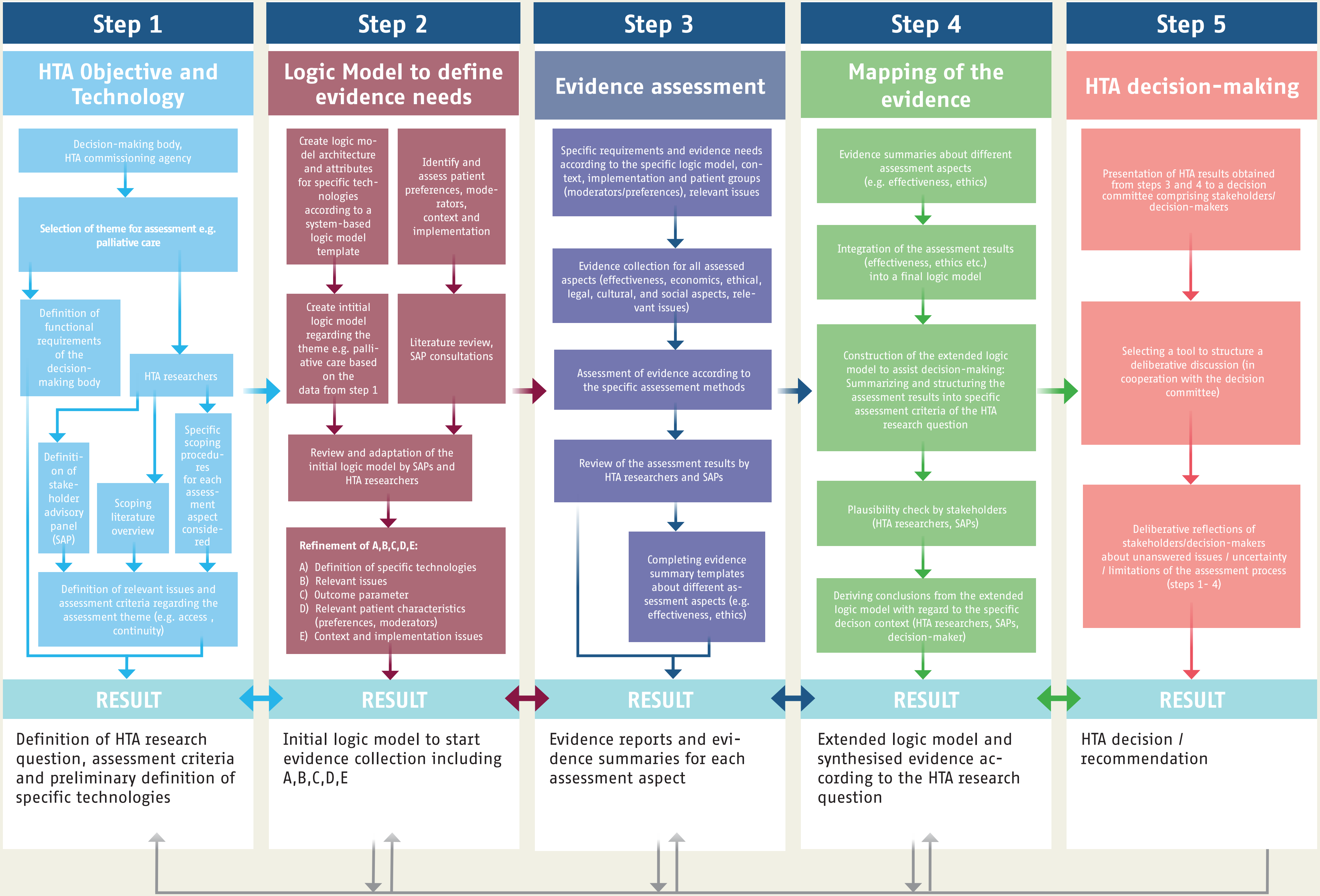
The INTEGRATE-HTA Model is built on a) the experiences of traditional HTA which mainly provides side-by-side assessments of the different aspects (for details see chapter 1.1.3); b) the methodological guidances developed in the INTEGRATE-HTA-project (for details see chapter 1.1.4); c) the dimension of information in HTA (see chapter 2.2) and d) the literature review on approaches for integration (for details see chapter 3). The involvement of stakeholder panels in each step of the assessment process provides the opportunity for clinical experts, academics, patients, as well as their families, and the public to contribute suggestions and give feedback to the HTA project team.

The INTEGRATE-HTA Model, which integrates the four dimensions of information in HTA, is shown in Figure 5. It comprises five steps:

Step 1	**Step 1:** Definition of the HTA objective and technology: The technology and objectives of the HTA are defined based on the input of stakeholder advisory panels (SAPs), a literature review and the specific scoping procedures of the assessment methods for each assessment aspect.
Step 2	**Step 2:** Creation of an initial logic model to define evidence needs: The initial logic model visualizes the HTA objective, including the definition of specific technologies, the relevant issues of interest, outcome parameters to be assessed, patient preferences and moderators, as well as context and implementation issues.
Step 3	**Evidence assessment:** The evidence for the different assessment aspects is collected and assessed.
Step 4	**Step 4:** Mapping of evidence: In step 4, the results of step 3 are processed and restructured to draw a model, which is an extended logic model to assist decision-making. Whereas the initial logic model in step 2 specifies what evidence is relevant to the HTA objective, the extended logic model represents the results of the assessments and visualizes the interrelationships to assist decision-making.
Step 5	**HTA conclusion:** At this stage, the assessment results are organized in a way suitable for presentation to decision-making bodies and other stakeholders interested in the results. Step 5 involves a structured decision-making process and is not an integral part of the HTA in a narrow sense.

The process of the INTEGRATE-HTA Model is iterative in nature, thereby allowing revisions where necessary. For instance, new data illustrated in the initial logic model (step 2) can necessitate modifications of the HTA objective that was defined in step 1. The INTEGRATE-HTA Model was applied in a case study on palliative care [see "Integrated assessment of home based palliative care with and without reinforced caregiver support: 'A demonstration of INTEGRATE-HTA methodological guidances"] (Brereton et al., 2016). The model was iteratively revised during the practical application. For each step of the INTEGRATE-HTA Model, an example from the case study on palliative care is provided. In the following sections, the five steps of the INTEGRATE-HTA Model are described in detail.

Figure 5: The INTEGRATE-HTA Model for an integrated assessment of complex technologies.



4.1 STEP 1: HTA OBJECTIVES AND TECHNOLOGY

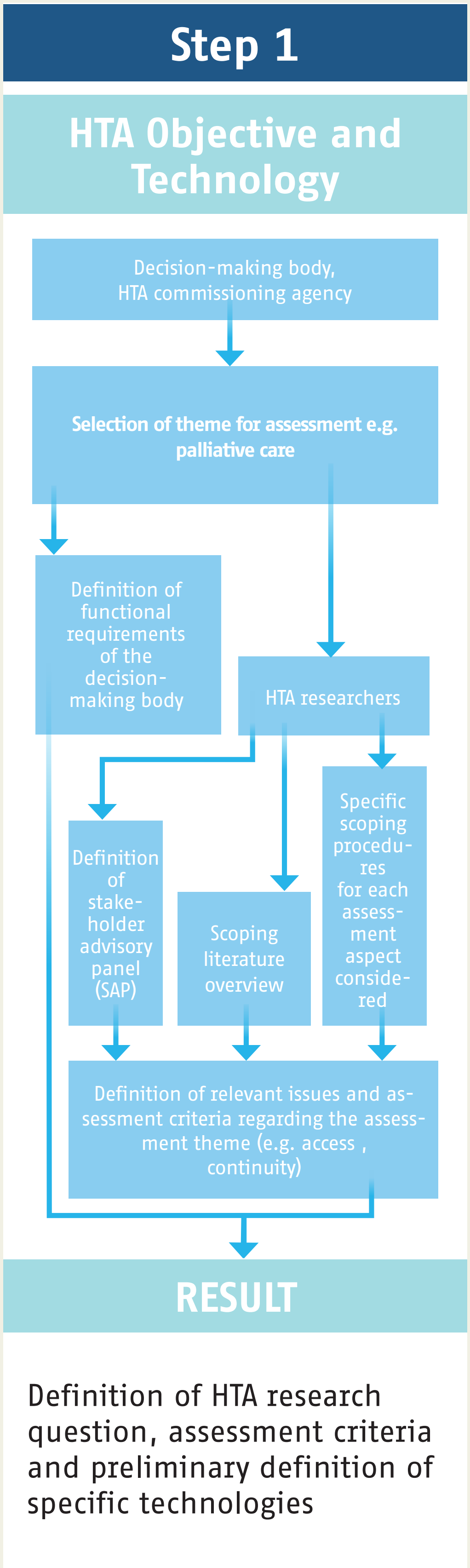
The first step of any HTA process is the definition of the assessment theme, in most cases the health technology to be assessed. However, the starting point might also be a specific health problem or the intention to rearrange a certain area of care. Usually the process is initiated by the decision-making body, (e.g. the health care authority), needing a decision on the issue. For an integrated assessment, we suggest that this decision-making body cooperates with an HTA agency to develop the 'terms of reference'. These 'terms of references' are developed according to the functional requirements of the decision-making body, a scoping literature overview of the assessment theme, scoping outcomes from the different assessment aspects such as economics and stakeholder input.

Stakeholder advisory panels (SAPs) are implemented to involve relevant stakeholders in the HTA process from the beginning (addressing dimension 4; chapter 2.2.1). The term 'panel' refers to the collective information provided by individuals or groups independent of their location, as patients and busy professionals cannot always attend face-to-face meetings, especially when stakeholders are geographically dispersed. Patients, their families, clinicians and academics have different types of expertise. Their contribution ensures that the results of the HTA are useful to both service users and providers. As a result of their experience, these lay and professional stakeholders contribute to the scope of the HTA, the selection and prioritization of specific issues, and the assessment criteria of the HTA research question.

In parallel, the scoping procedures of each assessment aspect (see "Guidance for assessing effectiveness, economic aspects, ethical aspects, socio-cultural aspects and legal aspects in complex technologies") (Lysdahl et al., 2015) can feed into the HTA objective. For instance, assessing the complexity of the technology of interest at the beginning of the ethical assessment can be part of the general information gathering in this initial step. An important aspect of this task is to elaborate on how the scopes of different assessment aspects are interrelated. Continuous collaboration between the various assessment aspects is essential to avoid overlaps from the beginning of the HTA (e.g. between the socio-cultural and the ethical assessment)."

In order to operationalize the objective of the HTA, defining assessment criteria is useful. Separating the HTA into clearly defined assessment criteria provides a basis for integration at the end of the assessment. The as-

Figure 6: Step 1: HTA Objectives and Tehnology.



sessment criteria can be selected from the scoping literature review on the assessment theme, a generic set of criteria (such as EVIDEM (Goetghebeur et al., 2008), the HTA core model (Lampe et al., 2009), or the criteria of existing decision committees such as NICE or the Dutch health care authority.

The definition of the assessment criteria should be in line with the values of stakeholders for the specific health technology. Stakeholders and decision-makers should come to a consensus on the definition and structure of the HTA research question, including the assessment criteria. In doing so, the values and preferences of participating stakeholders (dimension 4) integrate the different aspects that need to be assessed (dimension 1) from the beginning of the HTA.

The output of step 1 of the INTEGRATE-HTA Model is the identification of the HTA objective, including relevant issues, outcomes and the technologies to be assessed (e.g. models of care).

Example – HTA-Objectives and definition of the health technology in the INTEGRATE-HTA case study on palliative care

The objective of this case study was to compare reinforced models of palliative home care vs. non-reinforced models of palliative home care. SAPs from several European countries contributed to the HTA objective by providing 23 important general issues in palliative care (e.g. continuity of care, caregiver support). The HTA objective was separated into different assessment criteria. These criteria were defined and operationalized according to the glossary of the International Network of Agencies for Health Technology Assessment (INAHTA) and the Joanna Briggs Institute outlined in table 2. Step 1 resulted in the identification of the following HTA research question:

Table 2: Definitions of assessment criteria used in the HTA research question about reinforced models of home-based palliative care (International Network of Agencies for Health Technology Assessment (IANHTA), 2015; The Joanna Briggs Institute, 2014).

Criterion of interest	Description
Effectiveness	is defined as "The benefit (e.g. to health outcomes) of using a technology for a particular problem under general or routine conditions, for example, by a physician in a community hospital or by a patient at home." Clinical effectiveness is defined as "The extent to which a specific intervention, procedure, regimen, or service does what it is intended to do under ordinary circumstances, rather than controlled conditions. Or more specifically, the evaluation of benefit to risk of an intervention, in a standard clinical setting, using outcomes measuring issues of importance to patients (e.g. ability to do daily activities, longer life, etc.)".
Cost effectiveness	is defined as an economic evaluation consisting of comparing various options in which costs are measured in monetary units, then aggregated, and outcomes are expressed in natural (non-monetary) units.
Acceptability	is defined as being agreeable to defined population groups, often those benefiting from the technology, target groups affected by the intervention, those implementing an intervention, and society at large.
Meaningfulness	is defined as "the extent to which an intervention or activity is positively experienced by the patient. Meaningfulness relates to the personal experience, opinions, values, thoughts, beliefs and interpretations of patients or clients".
Appropriateness	is defined as "the extent to which an intervention or activity fits with or is apt in a particular situation." Clinical appropriateness is about how an activity or intervention relates to the context in which care is given.
Feasibility	is defined as "the extent to which an activity is practical and practicable. Clinical feasibility is about whether or not an activity or intervention is physically, culturally or financially practical or possible within a given context".

"Are reinforced models of home-based palliative care

- acceptable,
- feasible,
- appropriate,
- meaningful,
- effective, and
- cost-effective

for providing patient-centred home-based palliative care [compared to usual home-based care models of palliative care] in adults (defined as those aged 18 years and above) and their families?"[1]

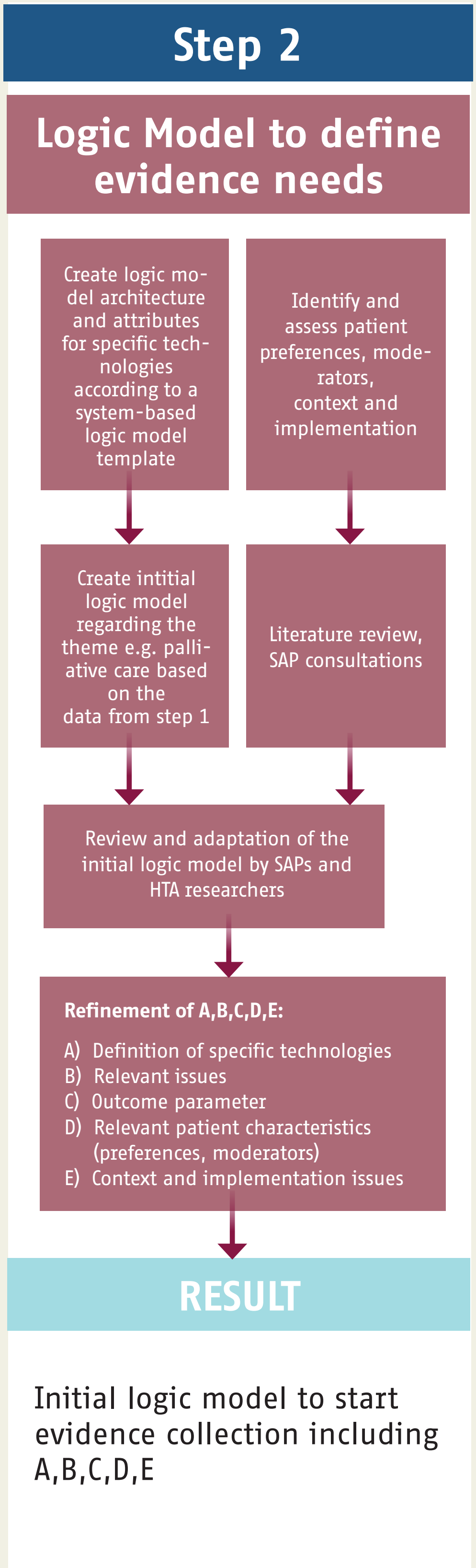
4.2 STEP 2: DEVELOPMENT OF INITIAL LOGIC MODEL TO DEFINE EVIDENCE NEEDS

The HTA objective, the generic logic model template and the relevant issues from the SAPs identified in step 1 are the basis of step 2. These inputs are integrated by using a qualitative modeling technique (see appendix, chapter 8.1.3) such as a logic model.

A system-based logic model template (see: "Guidance on the use of logic models in health technology assessment of complex interventions") (Rohwer et al., 2016) is applied and transformed into an initial logic model regarding the technology of interest. The template allows the identification of participants, interventions, comparators, outcomes, context, and implementation issues from a system perspective. The generic logic model used in the case study is illustrated in Figure 8.

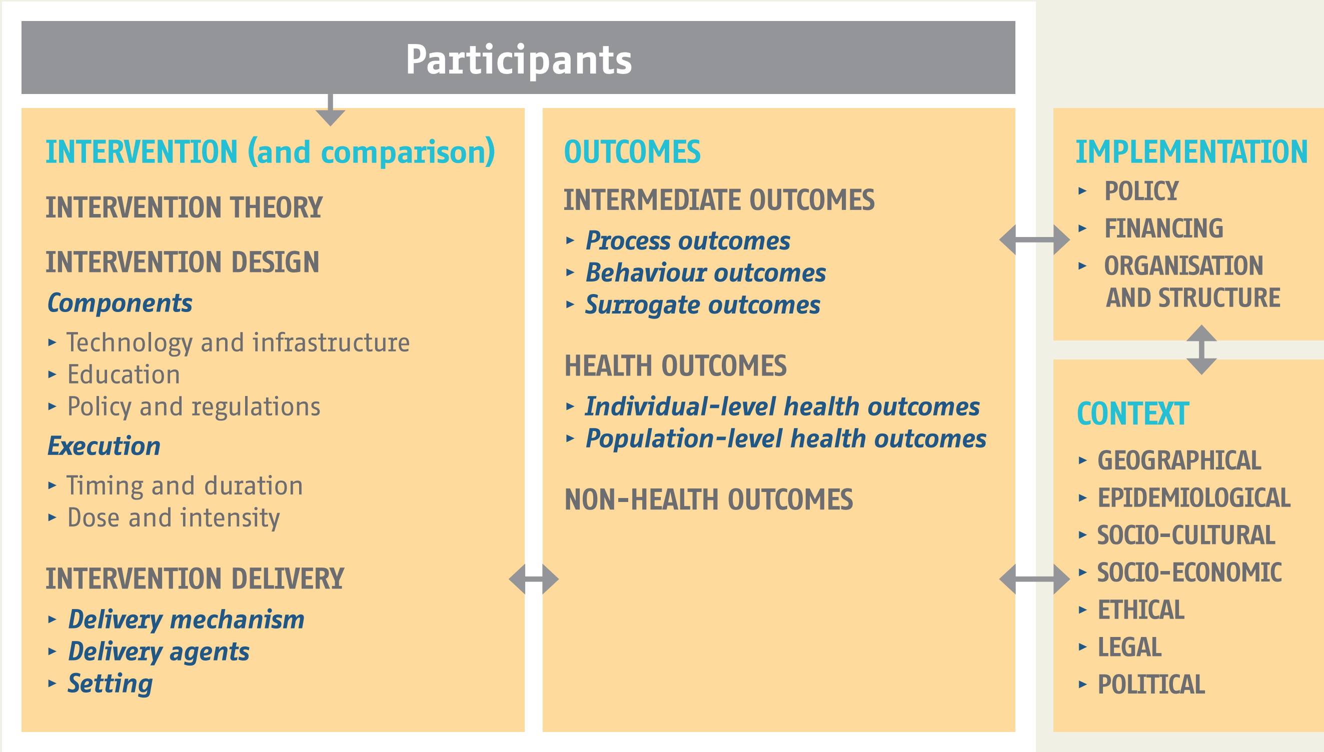
Thus, the architecture and structure of the generic logic model is adapted for the specific technologies of interest in accordance with the HTA objective (such as to compare reinforced vs. non-reinforced models of home based palliative care). The initial logic model resulting from this task aims to illustrate the system within which the interaction between the patient, the technology of interest, context, and implemen-

Figure 7: Step 2: Logic model to define evidence needs.



1 As this case study was not initiated by a decision-making body, our starting point was to assess models of palliative care. The literature review on models of palliative care identified reinforced models of home-based palliative care as one technology. Reinforced models of home-based palliative care were selected as they clearly address the SAP issue on caregiver support. This match between the results of the literature review (reinforced models) and the SAP issues (caregiver support) identified reinforced models of palliative home care as a (or the) technology of interest.

Figure 8: System-based logic model template.



tation issues takes place. Different inputs will feed into the initial logic model, from the first draft to the final version at the end of step 2.

The first draft of the initial logic model (see "Guidance on the use of logic models in health technology assessments of complex interventions") (Rohwer et al., 2016) is adapted based on scoping literature searches and expert consultations from step 1, in addition to brainstorming within the team. At the same time, relevant patient preferences and moderators are identified and assessed in accordance with the "Guidance for the assessment of treatment moderation and patients' preferences" (Van Hoorn et al., 2016). Context and implementation are assessed by the application of the "Guidance for the Assessment of Context and Implementation in Health Technology Assessments (HTA) and Systematic Reviews of Complex Interventions: The Context and Implementation of Complex Interventions (CICI) Framework" (Pfadenhauer et al., 2016). The assessment results regarding context, implementation issues and patient characteristics based on the literature and SAP consultations feed into the initial logic model. Thus, the assessment aspects (dimension 1) and modifying factors (dimension 2) are integrated within this logic model (Figure 7 as illustrating example).

The SAPs (dimension 4) contribute their perspectives regarding the contents of the initial logic model. The stakeholders and the HTA researchers review the initial logic model and provide feedback on its' plausibility. Accordingly, the HTA objective, including the definition of specific technologies, the relevant issues of interest, outcome parameters to be assessed, patient preferences and moderators, context and implementation issues, will be refined.

The output of this step is an initial logic model for the health technologies of interest. This logic model will be used as a conceptual framework to guide the data collection of individual assessment aspects (dimension 1) in step 3 (e.g. patient preferences can inform the search strategy for effectiveness outcome parameters).

If the logic model provides new aspects that need to be considered in the HTA objective, the research question can be iteratively revised from step 1. Step

Figure 9: Example: Initial logic model of reinforced and non-reinforced home-based palliative care.

Context

Epidemiological
- Cancer focused palliative care
- Other Diseases

Political
- –

Legal
- Mental capacity act
- Advanced Directives
- Shared decision-making

Socio-cultural
- Ethnicity
- Religion
- Individual patient preferences
- Family and community preferences

Ethical
- Autonomy
- Sanctity of Life
- Beneficence
- Non-maleficence
- Justice

Geographical
- Urban vs. rural
- European Union

Socio-economic
- Education
- Wealth
- Housing

Participants

- Patients: adults with life limiting conditions (malignant and non-malignant) receiving palliative care at home
- Lay caregivers: family members of patients or others (friends, neighbors) who may take on the role of lay caregiving (≥18 years)

Implementations

Policy
- Quality of care and service organisation strategies
- Financing/Reimbursement strategies

Funding
- Public (e.g. taxation; insurance)
- Private/ self-funding
- Third sector/charity

Organisation and structure
- Public sector
- Private sector
- Charitable/voluntary sector
- Integration/coordination of services
- Organisational culture

Provider
- Generalist and/or Specialist health and social care professionals
- Lay caregivers
- Others: Self-care, complementary and alternative therapists, charity workers/ volunteers
- Within-team coordination and continuation of care

Intervention

Intervention theory
- Holistic approach to improve quality of life and to enable a good death for patient
- Aim to allow the patient to be treated for and die at home, if desired
- (Reinforced) Explicit, structured support for the lay caregiver to alleviate burden due to caregiving

Components
- Services addressing physical, psychological, social and spiritual needs of patients
- (Reinforced) Services explicitly providing psychosocial or psychoeducational support to lay caregiver
- Active and reactive support

Execution
- Timing, duration and frequency
- May commence at any time from diagnosis to end of life and bereavement
- Models of transition to palliative care e.g. concurrent palliative and curative care; palliative care upon cessation of curative care

Delivery mechanisms
- Face-to-face /distant (telephone, online)/ mixed
- Individual/group/ patient-carer dyad/ mixed

Outcomes

Intermediate outcomes

Process outcomes
- Quality of care
- Hospitalisation
- Reach
- Professional caregiver outcomes

Surrogate outcomes (of patients and carers)
- Coping
- Mastery
- Self-efficacy

Health outcomes

Patients
- Quality of life
- Physical well-being (reduced symptoms)
- Psychological well-being
- Spiritual well-being
- Good death/achieving preferred place of death
- Survival

Lay caregivers
- Psychological health
- Physical health
- Quality of life

[1] includes short-, medium-, and long-term outcomes

[2] includes proxy outcomes (need to be indicated)

1 and step 2 of the INTEGRATE-HTA Model thereby define a comprehensive scope for the HTA.

Example – Specific logic model for the INTEGRATE-HTA case study on palliative care

A specific logic model was developed for reinforced and non-reinforced models of home-based palliative care as the technology and comparator of choice for the HTA research question. The information was assembled from consulting with the SAPs and consultation of palliative care literature and international palliative care experts. Figure 7 shows the specific logic model for reinforced and non-reinforced models of home-based palliative care (for details see: "Integrated assessment of home based palliative care with and without reinforced caregiver support: 'A demonstration of INTEGRATE-HTA methodological guidances") (Brereton et al., 2015).

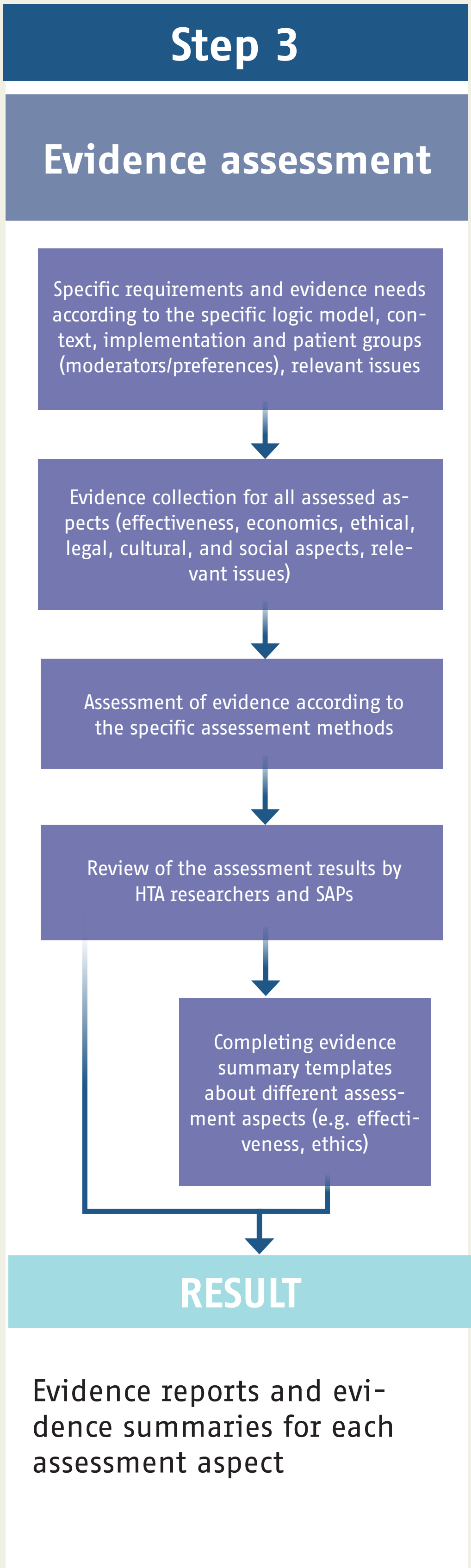
4.3 STEP 3: EVIDENCE ASSESSMENT

The initial logic model from step 2 is applied as a conceptual framework guiding the evidence assessment in step 3. The evidence is collected with reference to the identified patient preferences and moderators, context and implementation issues, relevant issues of interest (e.g. continuity of care), specific technologies and outcome parameters that are outlined in the logic model. The evidence assessment is guided by applying the methodological INTEGRATE-HTA guidances produced for specific assessment aspects (see "Guidance for assessing effectiveness, economic aspects, ethical aspects, socio-cultural aspects and legal aspects in complex technologies" (Lysdahl et al., 2015)).

Depending on the specific assessment aspects, there are various sources of evidence and scientific methods for the evidence assessment, such as meta-analysis for effectiveness outcomes or the Socratic approach for ethical outcomes. An important aspect of step 3 is to elaborate on how the different assessment aspects are interrelated. Continuous collaboration between the various assessment processes is essential to avoid redundancies (such as between the socio-cultural and the ethical assessment).

Finally, the assessment results are reviewed by HTA experts and SAPs (dimension 4). The outputs of step 3 are evidence reports for each assessment aspect (e.g. report on economics, report on ethical aspects, etc.). Thus, the evidence reports integrate the assessment results for individual aspects (dimension 1) and the

Figure 10: Step 3: Evidence assessment.



degree of uncertainty (dimension 3) that needs to be assessed.

Additionally, the HTA researchers present the assessment results for each assessment aspect as standardized evidence summaries. The evidence summaries are not primarily designed for presentation to stakeholders, decision makers or end users of HTA. The purpose of this tool is to provide a transparent and operational overview of the assessment results, which were structured according to assessment criteria of the HTA objective outlined in step 1. This tool is further described in the following section.

4.3.1 Completing the evidence summary template

4.3.1.1 Evidence Summaries

HTA researchers complete the evidence summaries to provide a concise overview of the results for each assessment aspect (i.e. regarding effectiveness, socio-cultural, ethical, economic and legal aspects, patient preferences, moderators, context and implementation issues). The evidence summaries separate the results for each assessment aspect into the outcomes that have been assessed following the similar concept of GRADE. We use the term "assessments results" for describing both quantitative assessment results (such as mortality, morbidity, quality of life for effectiveness) as well as qualitative assessment results (such as vulnerability as result of the ethical assessment). The evidence summary template is provided in the appendix (chapter 7.3).

The evidence summaries for each assessment aspect consist of 5 items as illustrated in Figure 11.

1. General importance of assessment aspect/ outcomes for health care: This item describes the overall importance of a certain aspect. A general description of the assessment aspect and the outcomes should be provided independent of the assessed technology.

   Example: If results of the effectiveness assessment are reported, the importance of effectiveness, including the outcomes assessed such as place of death in palliative care, needs to be described in a generic manner.

2. Specific importance of the assessment aspect/ outcomes in disease context: The importance of the assessment aspect and the related outcomes should be presented in the disease context (e.g. terminal diseases relevant for palliative care). The information should outline the relevance of the assessments results for the specific disease context, such as the severity of disease and the population affected.

Figure 11: Structure of HTA aspects for the evidence summary.

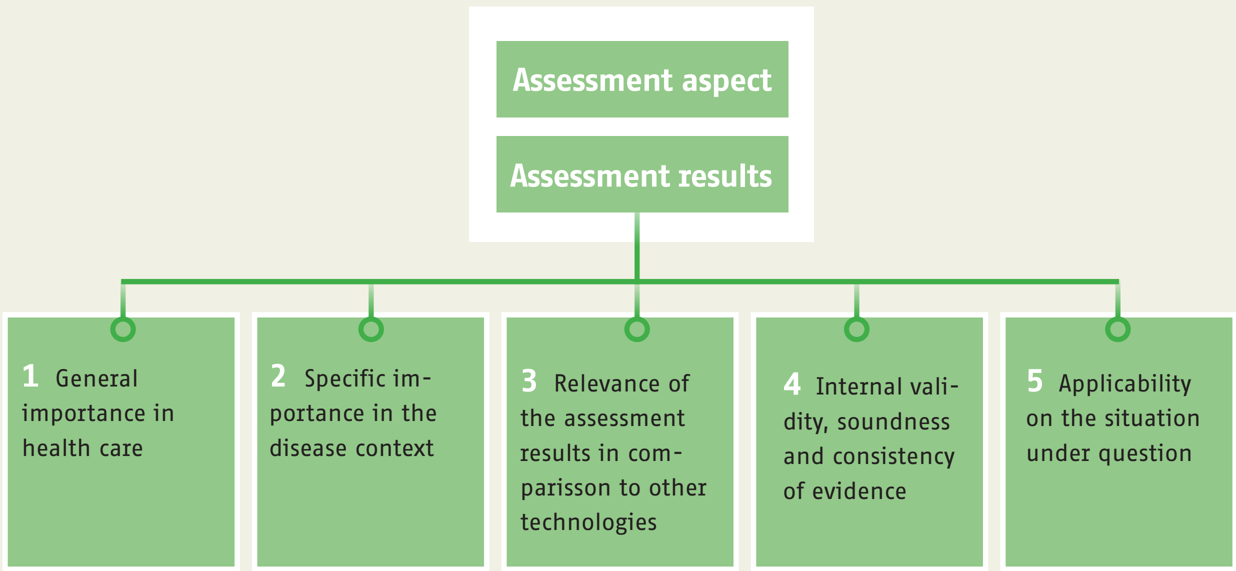


Table 3: Evidence summary template for each assessment aspect.

1 **General importance of assessment aspect for health care / General description of the assessed outcome**	
2 **Specific importance of the assessed outcome in disease context**	
3a **Relevance of each assessed outcome taking the technology of interest and a comparator into account (including effects for subgroups)**	
3b **Influence of modifying factors (context, implementation issues and patient characteristics) on the assessed outcomes**	
4 **Quantitative results: Internal validity, uncertainty and consistency of evidence / Qualitative results (ethics, socio-cultural, legal): Soundness**	
5 **Applicability to the situation under question / For Step 4: Assignment of the assessments results to the assessment criteria of the HTA research question**	

Example: Any improvement in pain reduction can be regarded as highly important because reducing pain represents an essential aspect for terminal conditions relevant for palliative care.

3. Relevance of assessments results taking the technology of interest and a comparator into account and including modifying factors: The outcomes of the assessment should be presented for both the technology of interest and the comparator, so that comparisons can be made (point 3a). This information should outline the magnitude of an effect (where possible) such as a benefit in survival of 6 months for the technology of interest vs. 3 months for the comparator. Additionally, the influence of modifying factors (context, implementation issues and patient characteristics) on the assessed outcomes should be outlined (point 3b).

   Example: The assessment of effectiveness showed a potential improvement in manageability for caregivers for reinforced models compared to home-based models (point 3a). As modifying factor, caregiver competence had a positive effect on caregivers' feeling of manageability (point 3b). Thus, it (should be) assessed whether inter ventions seeking to improve caregiver competence, e.g. the included COPE (Creativity, Optimism, Planning, and Expert Information) interventions, have a stronger effect for caregiver manageability than those reinforced models not aiming to improve caregiver competence.

4. Internal validity, soundness and consistency of evidence need to be openly reported. The evidence should be reported in line with scientific standards. This includes consideration of uncertainty (such as conflicting results across studies, limited number of studies and patients) and the extent to which reporting of evidence on the proposed technology is complete and consistent. For qualitative assessment aspects, the soundness of arguments needs to be considered.

   Example: Only two observational studies with limited statistical power could provide evidence for quality of life. As such, the internal validity of the evidence is low and this has to be considered during decision-making.

5. Applicability to the situation under question describes the extent to which evidence on the proposed technology is relevant for the decision setting (in terms of population, disease stage, comparator technologies, outcomes etc.).

   Example: Effectiveness outcomes of a particular study cannot be transferred to a specific decision context if the study population is significantly different (e.g. results from a palliative care study for children cannot be simply transferred to the care of adults).

4.3.1.2 Additional box as preparation for step 4

As outlined in step 1, the researchers responsible for the assessment of individual aspects of the HTA assigned their results to the assessment criteria of the HTA objective. For instance, "Vulnerability", as an assessment result from the ethical assessment, was assigned by the HTA researcher to the assessment criterion "Meaningfulness" of the HTA objective. A second researcher checks all assignments made to identify overlaps in the assessments results provided by evidence summaries from different assessment aspects (such as evidence for "patient autonomy" provided by both the legal and ethical assessments).

Example – Evidence Collection for the INTEGRATE- HTA case study on palliative care

Separate assessments were conducted for the specific assessment aspects. The evidence summary below (Table 4) illustrates the assessment results for the effectiveness of reinforced palliative home care for patients in the case study on palliative care (for details see: "Integrated assessment of home based palliative care with and without reinforced caregiver support: 'A demonstration of INTEGRATE-HTA methodological guidances'") (Brereton et al., 2016).

Table 4: Evidence summary for effectiveness on patient outcomes.

1 **General importance of assessment aspect for health care / General description of the assessed outcome**	Effectiveness describes the capacity of the assessed intervention to produce a desired (beneficial) change in signs, symptoms or course of the targeted condition, patient-reported outcomes (PROs) (e.g., quality of life, convenience to patient) and harmful or undesired health effects, compared to alternative interventions. **1.** Pain describes an unpleasant feeling associated with actual or potential tissue damage. Pain and relief therefrom is measured using a very wide range of scales and questionnaires. **2.** Symptom control describes the ability to control symptoms by the proposed intervention. Depending on the assessed condition, there is a large range of symptoms. **3.** Quality of life is the general/health related well-being of individuals. Quality of life is measured using a wide range of disease specific scales, questionnaires and tools. **4.** Psychological health describes the psychological well-being, or an absence of a mental disorder. Consequently, this may be measured through scales addressing depression, anxiety, worry, mood, etc. **5.** Death at home is generally measured as a proportion of those patients who died at home, compared to those who died in hospitals or nursing homes. **6.** Hospitalization is a measure of how much time a patient spends in the hospital. This can be as a proportion of total time spent in home-based care in the last 2 months, 1 month or 2 weeks of life. It can include all admissions to hospital or only emergency department visits. **7.** Response outcomes highlight which services empower patients to be more prepared patients through education and teaching, to improve self-care, problem-solving. **8.** Satisfaction with care measures how satisfied patients are with care, how well they perceive they are being cared for, and how effective they perceive care to be.
2 **Specific importance of the assessed outcome in disease context**	**1.** Pain – many palliative patients suffer from pain at the end of life. Considerable patient burden at the end of life may be due to pain, and it is therefore important for services to address this. **2.** Symptom control – similar to pain, palliative patients suffer from a range of symptoms at the end of life. It is important for patient-focused services to help relieve patients from the suffering due to symptoms. **3.** Quality of life – pain, symptoms, social and existential problems can significantly decrease quality of life at the end of life. Home-based palliative care services should improve quality of life by relieving pain and symptoms, as well as allowing patients to remain at home should they so wish. **4.** Psychological health – pain, symptoms, social and existential problems may lead to a grave psychological burden for patients. As problems experienced at the end of life negatively influence psychological health, how services work to counteract this effect should be measured. **5.** Death at home – home-based services should aim to help patients die at home should they so wish. **6.** Hospitalization – home-based services should aim to help patients remain at home during the end of life should they so wish. Patients should be enabled to spend more time at home during the end of life. **7.** Response – If interventions aim to empower palliative care patients by teaching them certain skills, the effectiveness of this should be measured. **8.** Satisfaction – if patient perception of home care is important for effectiveness, then this should be investigated.

3a Relevance of each assessed outcome taking the technology of interest and a comparator into account (including effects for subgroups)	**1.** Pain – Only one study measured patient pain, and the intervention had a neutral effect. **2.** Symptom control – 5 studies measured patient symptom control; 2 of these showed a beneficial intervention effect, and 3 showed a neutral effect. **3.** Quality of Life – measured in 3 studies, all of which showed a neutral effect. **4.** Psychological health – 2 studies provided 4 measures; 2 showed a beneficial intervention effect and 2 a neutral effect. **5.** Death at home – No studies measured death at home. **6.** Hospitalization – measured in 2 studies, both of which showed a neutral effect. **7.** Response – 2 studies provided 3 measures; all of which showed a neutral effect. **8.** Satisfaction – measured in 1 study, which showed a neutral effect.
3b Influence of modifying factors (context, implementation issues and patient characteristics) on the assessed outcomes	**Moderators of treatment outcome:** Few studies identified in the literature discussed moderators relating to caregivers; some evidence pointed to the fact that caregiver competence had a positive effect on caregivers' feeling of manageability. From the subset of interventions included in the effectiveness assessment, those known as COPE (Creativity, Optimism, Planning, and Expert Information) interventions, were designed to help caregivers develop skills and competencies for caregiving. Because of this, a post hoc subgroup analysis was performed, assessing whether COPE interventions improved caregiver outcomes. With the limited evidence available, however, no visible difference in effectiveness trend seems present between COPE and non-COPE interventions. **Context:** The geographical domain of context, e.g. whether patients and caregivers are located in urban or rural areas, is potentially also a modifying factor for effectiveness. We, therefore, performed a post hoc subgroup analysis, by separating studies based on whether they were conducted with patients and caregivers from urban or rural areas. Only 2 out of the included 10 studies explicitly enrolled participants from rural areas, but in both of these studies, a majority urban participants was also included. This in itself is a result, and highlights the need for the implementation and evaluation of such programs in rural areas.
4 Quantitative results: Internal validity, uncertainty and consistency of evidence **Qualitative results (ethics, socio-cultural, legal): Soundness**	**Internal validity:** Most of the included studies are RCTs, but as common in palliative care research, investigators had significant problems in recruiting and retaining patients in the trials. Further, earlier than expected death led to low power in many of the studies. The criteria used to judge risk of bias were taken from the Cochrane Effective Practice and Organization of Care (EPOC) Group (see full evidence report for more details). **Uncertainty:** Only 6 studies measured patient outcomes, and 5 of those only measured a narrow range of outcomes. Certain outcomes, which may be considered important – e.g. the effect on patient satisfaction with care, the effect on hospitalization and death at home – were measured very rarely, if at all. The effects of included reinforced services on these outcomes remain uncertain. **Consistency:** Little consistency is seen as most of the evidence points towards a neutral effect, with the rest mainly favoring the intervention. There is little evidence (1 study for 1 outcome) pointing towards an effect favoring the control.
5 Quantitative results: External validity of evidence, generalizability, applicability or **Qualitative results (ethics, socio-cultural, legal): Relevance**	The evaluated reinforced and non-reinforced services were implemented in a variety of settings – with regard to country, geography, healthcare system. How this would influence the implementation of certain services in England should be considered. A few studies included in the effectiveness assessment were conducted in England, and the evidence from these studies should be generalizable to the rest of England.
For Step 4: Assignment of the assessment results to the assessment criteria of the HTA research question	All assessment results should be assigned to the assessment criterion "Effectiveness".

4.4 STEP 4: MAPPING OF THE EVIDENCE

Step 4 processes and organizes the assessment results that have been generated in step 3 of the INTEGRATE-HTA Model. The evidence summaries from step 3 are assigned to the respective assessment criteria of the HTA objective (such as "Meaningfulness", "Acceptability" see 4.3.1.2). Finally, the initial logic model created in step 2 provides the structure for the extended logic model to assist decision making. The extended logic model to assist decision making is a new tool that was developed in this project to enable a comprehensive, transparent and integrated illustration of all assessment results. It is a graphical way of informing decision makers about aspects related to the technologies of interest and identified as relevant for their benefit according to the HTA objective. The following sections describe how the assessment results are restructured (4.4.1) to construct the extended logic model to assist decision making (4.4.2).

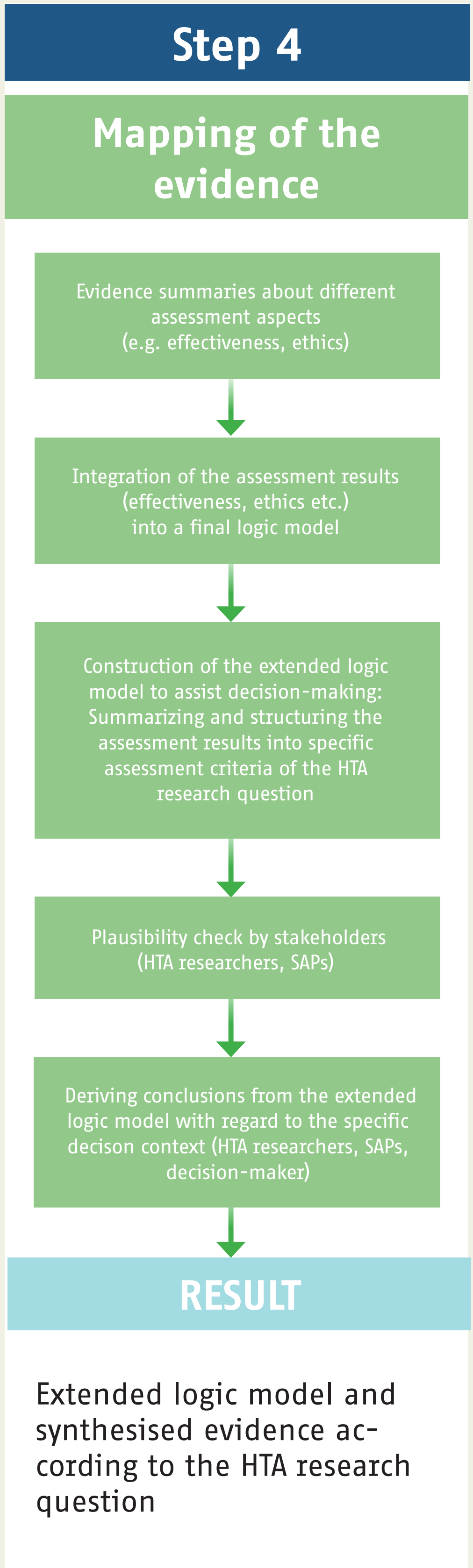
4.4.1 Integration of the assessment results into the final logic model

The assessment results are entered into the initial logic model from step 2, to obtain a final logic model. Where an assessment result consists of evidence from more than one assessment aspect (such as evidence for "patient autonomy" was provided by the legal and ethics assessments), it is assigned to multiple areas in the final logic model (in this case, the legal and ethical context).

4.4.2 Construction of the extended logic model to assist decision-making

HTA researchers process the evidence summaries from step 3 to provide integrated answers to the HTA objective. In step 3, the HTA researchers assign the assessment results from the evidence summaries to the relevant assessment criteria of the HTA objective defined in step 1. A summary table for each assessment criterion of the HTA objective is developed. For each summary table, the "Guidance on choosing qualitative evidence synthesis methods for use in health technology assessments of complex interventions" (Booth et al., 2016) supports the synthesis of the evidence obtained from the various assessment aspects. As a result,

Figure 12: Step 4: Mapping of the evidence.



the summary tables provide decision makers with a concise overview of the assessment results that specifically answer the HTA objective (illustrating example in Figure 13).

The summary tables and the final logic model provide the structure of the extended logic model to assist decision-making. In addition, the assessment criteria of the HTA objective feed into the extended logic model. The criteria are coded with symbols at the bottom of the extended logic model to assist decision-making. All assessment results relating to the same assessment criterion are coded with the same symbol (Illustration example: Figure 10). If an assessment result is assigned to multiple assessment criteria of the HTA objective (as outlined in 4.3.1.2), it will be coded with multiple symbols accordingly.

4.4.3 Plausibility check

Finally, the extended logic model should be presented to the SAPs (representing dimension 4) who should be asked about the plausibility and the usefulness of information provided. The feedback should feed into the final version. The summary tables (4.4.2) should be read in conjunction with the extended logic model to assist decision-making.

4.4.4 Conclusions derived from the extended logic model to assist decision-making

Presented as a "Table of content" of the assessment results, the extended logic model to assist decision-making (step 4) and the evidence reports (step 3) enable a detailed evaluation of benefits and drawbacks of each assessed technology. In addition, the extended logic model can be used for a structured applicability assessment regarding the implementation of the health technology in a specific setting (Brereton et al., 2015). The extended logic model thereby outlines the contextual and implementation factors, which will have been identified for the various HTA aspects in steps 2 and 3 of the INTEGRATE-HTA Model. The SAPs can evaluate these factors regarding the applicability and transferability of the health technology to a specific setting.

Example – Processing the Evidence in the INTEGRATE-HTA case study on palliative care

The assessment results were extracted from the evidence summaries of the different assessment aspects (e.g. effectiveness, legal aspects, etc.; example in step 3) and were assigned to the six assessment criteria of this specific HTA objective (see Figure 13). The HTA objective for the case study on palliative care was: "Are reinforced home care models of palliative care acceptable, feasible, appropriate, meaningful, effective, cost-effective for providing patient-centred palliative care [compared to usual home care models of palliative care] in adults (defined as those aged 18 years old and over) and their families?"

Finally, the assessment results were visualized in the extended logic model to assist decision-making as presented in Figure 14. For instance, the assessment result "Autonomy and shared decision-making" was dealt within three different assessment aspects (legal, ethics, socio-cultural aspects) and one modifying factor (patient preferences).

The assignment of assessment results to certain assessment criteria is coded with symbols:

□ Effectiveness = square;

☆ Cost-effectiveness = star;

△ Acceptability = triangle;

○ Meaningfulness = circle;

◇ Feasibility = diamond;

⬠ Appropriateness = pentagon

In addition, the sources of evidence are outlined using numbers:

1 = Guidance for the assessment of effectiveness, and economic, ethical, socio-cultural, and legal issues of complex technologies

2 = Guidance for the assessment of treatment moderation and patients' preferences

3 = Guidance for the Assessment of Context and Implementation in Health Technology Assessments (HTA) and Systematic Reviews of Complex Interventions: The Context and Implementation of Complex Interventions (CICI) Framework

Figure 13: Assignment of the assessment results to the assessment criteria of the HTA objective.

EFFECTIVENESS

- Caregiver
- Quality of life
- Response Outcomes
- Satisfaction with care
- Psychological health (plus preferences)
- Patients
- Pain
- Symptom control
- Quality of life Psycological health
- Hospitalisation
- Response
- Satiscfaction with care
- Death at home (plus preferences)

ECONOMICS

- Costs per patient
- Resources impact (e.g. Specialist Nurse time)
- Budget impact

ACCEPTABILITY

- Changing roles and relationships for caregiver (ethical)
- Changing roles and relationships for patients (ethical)
- Autonomy and shared decision making (legal, ethical, preferences)
- Location of death (preferences)
- Preference for survival

MEANINGFULNESS

- Vulnerability (ethical)
- Perceived usefulness and the idea of benefit (socio-cultural)
- Knowledge and understanding of the technology (i.e. home-based palliative care, socio-cultural)
- User-professionals-relationships and decision making (socio-cultural)

FEASIBILITY

- Context and implementation issues

APPROPRIATENESS

- Access and availability (ethical)
- Voluntariness (ethical)

Figure 14: Extended logic model to assist decision-making on reinforced models of home-based palliative care.

Context

Epidemiological
- –

Political 3
- Access and availability to health care (ethics, socio-economic, geographical, political)

Legal 1
- Autonomy and shared decision making (legal, ethics, preferences)

Socio-cultural
- User-professionals-relationships and decision making 1,3
- Autonomy and shared decision making (legal, socio-cultural, preference 1,3
- Knowledge and understanding of the technology 1
- Perceived usefulness and the idea of benefit 1

Ethical
- Changing roles and relationships for caregiver 1
- Changing roles and relationships for patients 1
- Autonomy and shared decision making (legal, socio-cultural, ethics, preferences) 1,3
- Access to, and availability to health care (ethics, socio-economic, geographical, political) 1,3
- Voluntariness 1
- Vulnerability 1

Geographical
- Infrastructure 3
- Access to, and availability to health care (ethics, socio-economic, geographical, political) 3

Socio-economic
- Access to, and availability to health care (ethics, socio-economic, geographical, political) 3
- Socio-economic status of recipient of care 3
- Economic climate 3

Participants

Patients, informal caregivers

Moderators for
- Patients: Death at home (outcomes, preferences) 2
- Caregiver: Psychological health (preferences, outcomes) 2

Preferences for
- Autonomy and shared decision making (legal, socio-cultural, ethics, preferences) 2
- Location of death 2
- Preference for survival 2

Implementation

Funding 1,3
- Financial support of informal caregiver
- Availability of resources for care provision
- Not being worth the investment

Organisation and structure 1,3
- Continuity of care
- Supervision and guidance

Policy 1,3
- Meeting a society`s demands
- Faciliation of death at home
- Navigating the health care system
- Social protection of informal caregver

Provider 1,3
- Characteristics of provider
- Team dynamics
- Interaction with care recipients
- Training needs

Intervention

Intervention Theory, aim & scope
- Holistic approach to improve quality of life and to enable a good death for patient
- Aim to allow the patient to be treated and die at home, if desired
- Explicit, structured support for the lay caregiver to alleviate burden due to care-giving

Components
- Services addressing physical, psychological, social and spiritual needs of patients
- Services explicitly providing psychosocial or psychoeducation al support to lay caregiver

Execution
- Timing, duration and frequency
- May commence at any time from diagnosis to end of life and bereavement
- Models of transition to palliative care e.g. concurrent palliative and curative care; palliative care upon cessation of curative care

Delivery agent 3
- Generalist and/or Specialist health and social care professional
- Lay caregivers
- Others: Self-care, complementary and alternative therapists, charity workers/volunteers

Delivery mechanisms
- Face-to-face /distant (telephone, online)/ mixed
- Individual/ roup/patient-carer dyad/mixe

Outcomes

Health outcomes 1

Caregiver
- Quality of life
- Response Outcomes
- Satisfaction with care
- Psychological health (outcomes, preferences)

Patients 1
- Pain
- Symptom control
- Quality of life
- Psycological health
- Hospitalisation
- Response
- Satisfaction with care
- Death at home (outcomes, preferences)

1
- Costs per patient
- Resources impact (e.g. Specialist Nurse time)
- Budget impact

EFFECTIVENESS | ACCEPTABILITY | FEASIBILITY | ECONOMICS | MEANINGFULNESS | APPROPRIATENESS

Key to numbers assigned within the symbols: Evidence informing the extended logic model resulted from the application of the following guidance: 1 = Lysdahl et al. (2016a) 'Guidance for assessing effectiveness, economic aspects, ethical aspects, socio-cultural aspects and legal aspects in complex technologies. [Online]. Available from: http://www.integrate-hta.eu/downloads/ 2 = Van Hoorn, et al (eds.) (2016a) Guidance for the assessment of treatment moderation and patients' preferences [Online]. Available from: http://www.integrate-hta.eu/downloads/ 3= Pfadenhauer et al. (2016) Guidance for the Assessment of Context and Implementation in Systematic Reviews and Health Technology Assessments (HTA) of Complex Interventions: The Context and Implementation for Complex Interventions (CICI) Framework [Online]. technology assessments of complex interventions & Rohwer et al. (2016) Guidance: Use of Logic Models in Health Technology Assessments of Complex Interventions [Online]. Available from: http://www.integrate-hta.eu/downloads/

4.5 STEP 5: HTA DECISION-MAKING

The purpose of this step is to analyze the HTA results in order to come to a decision. The decision making process should be performed by a decision panel including the HTA commissioners and the corresponding decision-making body, and possibly the stakeholders involved in the HTA process.

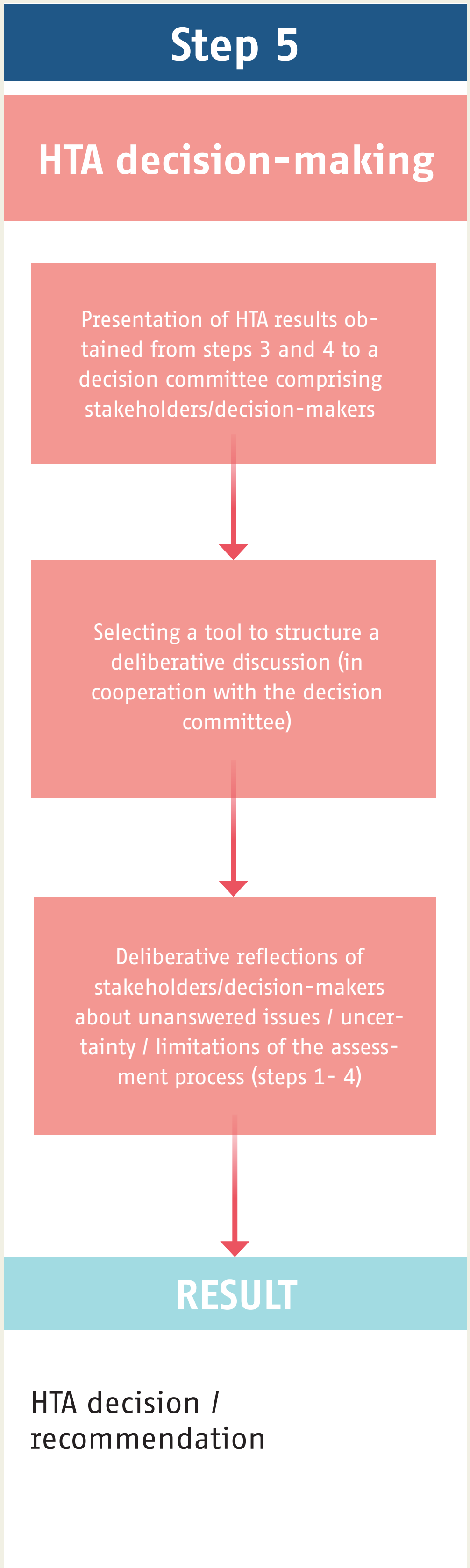
This final step is based on the evidence reports (step 3) and the visualization of the extended logic model to assist decision-making in step 4, including the HTA conclusions derived from the model and an analysis in terms of the performance of the health technology on the different assessment criteria of the HTA objective. It should support the members of the decision panel (dimension 4) to conduct a deliberative discussion. As such, the decision committee should actively reflect on the assessment results of the different assessment aspects (dimension 1), the degree of uncertainty (dimension 2) and the impact of the modifying factors (dimension 3) that are relevant for their specific decision context.

A decision support tool can be employed to structure the discussion of the decision committee. There are quantitative methods available, such as MCDA methods, or qualitative approaches such as consensus reaching processes. A combined approach, where a quantitative tool can be applied to certain aspects to prepare a qualitative discussion can also be envisaged. Flexibility in the application of these tools is crucial, taking different decision settings and evidence needs into consideration.

(a) MCDA approaches can be used to quantify the importance of the assessment criteria and the relevance assigned to specific assessment results (see integrative technique 5 in the appendix). MCDA in this case would not be used as a formula to come to a decision, but rather as a tool to make the values and viewpoints of decision makers transparent and support reflection on their preferences related to the range of dimensions in the overall assessment of a technology (Wahlster et al., 2015a).

(b) Several approaches to guide deliberative decision-making processes e.g. consensus reaching processes were identified. Consensus Reaching Processes (DeGroot, 1974; Eisenberg & Gale, 1959; Palomares et al., 2014) describe a variety of methods to measure the distances between different expert opinions or between individual and collective opinions. A feedback mechanism intends to

Figure 15: Step 5: HTA decision-making.



decrease these differences (numerical, intervals or linguistic) to achieve consensus for the final HTA decision.

Furthermore, the evidence that is restructured into summary tables according to the assessment criteria of the HTA objective (see 4.4.2) provides an additional structure for the final deliberative discussion. Based on these outputs, the SAPs can focus on the results assigned to one assessment criterion at a time. Following this, the decision panel can reflect on unanswered issues (perhaps because these issues won't have been raised yet), limitations of the HTA methods used, the HTA process applied, and uncertainty surrounding the HTA results. In keeping with step 1, this final discussion is flexible to allow adaptation of the decision-making process to different political decision settings in different countries. All dimensions are integrated to obtain a final HTA decision at the end of this step.

Example – Decision-Making in INTEGRATE-HTA case study on palliative care

For step 5 of the INTEGRATE-HTA case study, we selected a simple MCDA approach (based on the EVIDEM rating methods). Different lay and professional stakeholders with different backgrounds (e.g. physicians, service commissioners, former caregivers) joined a mock decision meeting. Based on the MCDA results, the participants identified important issues regarding HTA recommendations about reinforced models of palliative home care in the final deliberative discussion (for details see "Integrated assessment of home based palliative care with and without reinforced caregiver support: 'A demonstration of INTEGRATE-HTA methodological guidances") (Brereton et al., 2015).

5 CONCLUSIONS

The final impact of a complex health technology is affected by a broad range of interacting factors. These factors include effectiveness, economic, socio-cultural, legal and ethical aspects, as well as patient characteristics and context and implementation issues. An integrated perspective on these assessment aspects is important for the appraisal in health care decision-making.

We developed the INTEGRATE-HTA Model to address these issues. The model comprises five steps: After an initial definition of the HTA objective and the technology in accordance with the support of the stakeholders in step 1, the initial logic model in step 2 provides a structured overview of the factors and aspects around the technology. Patient characteristics, context and implementation issues feed into the assessment of effectiveness, and economic, ethical, legal, and socio-cultural aspects. Results of the assessments are structured by the HTA objective and feed into the extended logic model to assist decision-making. Finally, the results presented in this way form the basis of a structured decision-making process.

5.1 STRENGTHS AND LIMITATIONS OF THE INTEGRATE-HTA MODEL

The strength of the INTEGRATE-HTA Model is that it addresses all relevant dimensions of information in HTA of complex technologies, and that it frames integration throughout the assessment process and not only at the end. It addresses the methodological and content-related interdependencies between the different assessment aspects, taking patient characteristics, implementation issues and context and the uncertainties of information (dimension 3) into consideration. Stakeholders' values and information needs (dimension 4) are integrated in each step of the INTEGRATE-HTA Model. The participation of stakeholders throughout the INTEGRATE-HTA Model also ensures comprehensiveness and relevance of the results.

Our approach has some limitations. Usually HTA values rigid protocols and pre-defined objectives. In our model (sub-) objectives might need adaption during the process. Hence, the model needs time, expertise in different areas, major coordination and communication skills, flexibility, and building up a network with stakeholders. The success of integration is limited by the extent to which different assessment methods are harmonized to each other. The terminology and definitions used need to match between the assessment methods to truly integrate the assessment results.

In sum, we expect that the INTEGRATE-HTA Model can be applied for the assessment of most complex technologies in various health care systems and settings.

5.2 OUTLOOK

The INTEGRATE-HTA Model applies different integrative techniques to address various methodological, structural and organizational challenges associated with an integrated assessment of complex technologies. The INTEGRATE-HTA Model can feed into the further development of HTA processes of complex technologies. The more complex future health technologies will get, the more issues about integration of information will gain further importance. One of the next steps will be the application of the model to another complex technology.

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8 APPENDIX

8.1 MAPPING REVIEW ON INTEGRATION

A mapping review was conducted to identify integration methods to integrate the different dimensions of information in HTA. As in all systematic reviews, the search strategy is systematic to fully cover the field of literature. In contrast to systematic reviews, mapping reviews however do not require a formal quality assessment for included studies or a specific tool for the synthesis and analysis of the results.

8.1.1 Methods of the mapping review

Information sources and search

We searched the Web of Science; Medline, PsycINFO and the non-medical databases Econlit, ASSIA, International Bibliography of the Social Sciences and Sociological abstracts for the period January 2004 to April 2014. Keywords used were "Decision Support Techniques/ or *Decision Making"; "evidence* or perspective*"; "multi or context"; "criteria or element* or component* or attribute*"; "ethics or bioethics or equity or justice"; "societal or cultural" "concern* or norm*"; "preference* or point of view"; "integrat*"; "issue* or priorit* or aspect* or* process* or concept* or tool* or technique* or approach* or framework* or consider*"; "Resource Allocation/ or *Health Priorities/ or *Health Rationing"; "priorit* or decision* or coverage or policy or ration* or resource* or choice* or deliberat* or iterat* or panel or assumption*".The keywords were adapted to each database. Additional articles were found in the references and citations of the retrieved articles.

Study selection

The title and abstracts of all retrieved articles were reviewed in the first instance by PW. Where the decision about inclusion was unclear, a second researcher (AG) was involved. Inclusion criteria used are listed in table 5.

Methods were appraised with respect to their applicability to HTA. The categories of the data extraction form address the four dimensions in HTA that need integration (chapter 2.2).

Data collection process and data items

The date extraction table 8 guides the selection of methods as well as the mapping of the included methods. The template for data extraction was pre-tested using a sample of studies before full data extraction was initiated. Several publications could be used for referencing a particular method in the data extraction. Additional papers were retrieved if the description of a particular method was not sufficient.

Reporting of Results – integration methods

After completing the data extraction, a narrative synthesis was compiled according to the objective to present a comprehensive and practical overview of how to cover different dimensions of integration in HTA. Methods were described to obtain a general overview. By doing this, a map of integration methods was obtained.

Synthesis of results –fields of application for integration

Afterwards, the methods were systematically disaggregated to identify areas of application for integration (Table 9). The identified areas of application in HTA highlight similar means of integration in different methods. These areas of application provide guidance on suitable combinations of different methods.

8.1.2 Results of the mapping review: integration methods

The 30 methods identified from the mapping review include 7 (23%) qualitative, 14 (46%) quantitative and 9 (31%) mixed methods. We categorized the methods into four main categories: MCDA

Table 5: Inclusion criteria.

No	Category	Criteria
1	Year of release	January 2004- April 2014
2	Assessment topic	Medical and non-medical decision problems
3	Framework	Methods (concepts / approaches/ frameworks / models) including multiple, quantitative or qualitative aspects
4	Dimensions in HTA	Address dimensions in HTA (categories of the data extraction framework about integration)
5	Integration	Approaches that describe how (the process) these relevant issues should be considered: Should include connective elements to merge/ aggregate/ address interdependencies between aspects
6	Type of article	Articles that describe/apply a certain method
7	Source of publication	Peer reviewed journals and websites of health care authorities
8	Language	English, German

methods, analytic methods, preference elicitation methods, and consensus methods.

A description of all methods is provided in table 6 below.

8.1.3 Areas of application - extracted from the methods identified

The areas of application describe common patterns of integration in different methods and provide guidance on suitable combinations of different methods. The 9 areas of application are partially overlapping e.g. the techniques 1, 2, 3 and 6 are overlapping regarding the structure of decision criteria (Table 7 below).

Technique 1: Structuring of an HTA question into assessment criteria:

The separation of an HTA objective into clearly defined assessment criteria provides a basis for integration at the end of the assessment that was derived from MCDA methods. A clear definition and structure of the assessment criteria is important to assign assessment results (dimension 1) to certain criteria, such as "Meaningfulness" as one assessment criterion for the HTA case study on palliative care that was addressed by several assessment aspects e.g. patient characteristics, socio-cultural, legal aspects.

The assessment criteria of the HTA research question can either be presented alongside each other, structured in a hierarchy or a network (e.g. effectiveness in palliative care can be hierarchically structured into effectiveness for patients and effectiveness for caregiver with different outcome parameters for both groups). Alternatively, the ANP (Analytic Network process) describes a quantitative approach which structures criteria into a network to illustrate the interdependencies between them (Saaty, 2004). In this way, potential overlaps between different

Table 6: Description of all methods identified in the systematic review.

MCDA methods

- **Value based methods** calculate a value estimate for each decision option. Low performance on one criterion can be outweighed by higher performance in another criterion.

AHP (Analytic hierarchy process) (Hummel et al., 2012; Liberatore & Nydick, 2008; Saaty, 1977) starts by dividing the decision problem into different assessment criteria. These criteria are arranged into a hierarchy with main criteria and sub criteria. Following this arrangement, participants can perform trade-offs between the criteria by using a pairwise comparison between criteria on a 17-point-scale. Afterwards the trade-offs are entered into matrices and calculated by the eigenvector approach. The outputs of these calculations are value estimates for each decision option. These calculations include the calculation of an inconsistency score to trigger consensus among participants. When significant inconsistencies are observed, decision-makers can review their ratings. One theoretical problem regarding AHP which needs mentioning is the rank reversal issue. This means that the extension of the list of decision options by one additional option can cause a reversal of the ranking of two other options that are not related to the new additional decision option in any way.

ANP (Analytic Network process) (Saaty, 2001; Saaty, 1996) is similar to AHP. The major difference is that in ANP the criteria are structured as a network, and not as a hierarchy. Consequently, the weighting and scoring procedure becomes more complex, resulting in a supermatrix to additionally assess the interdependencies of criteria. The major advantage of ANP is that the network structure quantifies the interdependencies between different criteria.

REMBRANDT (Ratio Estimation in Magnitudes or deci-Bells to Rate Alternatives which are Non-DominaTed) (Lootsma, 1992) was developed to overcome some of AHP's theoretical problems, such as the rank reversal issue. The method provides a direct rating system on a logarithmic scale from +8 to -8, depending on which of the two criteria being compared is preferred over the other. The advantage of this logarithmic scale is that the calculations of the value estimate are simplified. Whereas AHP needs to calculate the eigenvector, REMBRANDT uses the geometric means from the pairwise comparison matrices for the final ranking of the decision options.

MACBETH (Measuring Attractiveness by a Category Based Evaluation Technique) (Bana E Costa & Vansnick, 1999) is another variation of the AHP. Following the basic principles of AHP, participants perform pairwise comparisons between 2 criteria on a simplified scale from 1 to 6, with 1 indicating a very weak difference between two criteria, and 6 an extreme difference.

EVIDEM (Evidence based decision-making) (Goetghebeur et al., 2012; Goetghebeur et al., 2008; Goetghebeur et al., 2010; Miot et al., 2012; Tony et al., 2011) consists of 15 core criteria that are specific for HTA decision-making, such as severity of disease. EVIDEM provides several weight elicitation methods. The most popular technique is the direct weighting approach, which is mostly used with a scale from 1 to 5. Firstly, the 15 core criteria are weighted independent of the assessed technology. Secondly, the performance of the technology is scored against each core criterion. Thirdly, a value estimate is calculated by combining weights and scores. Other options are point allocation, ranking in a hierarchical structure, pairwise comparison in a hierarchical structure, similar to the AHP rating, or best-worst scaling.

Swing weighting method (Belton & Stewart, 2002) and SMARTS (Simple Multi-Attribute Rating Technique Using Swings) (Edwards & Barron, 1994b; Edwards & Barron, 1994a; Winterfeldt & Edwards, 1993) are an advancement of the direct weighting approach using swing weights. Whereas weights in direct weighting reflect only the importance of a criterion, swing weights reflect both the importance of a criterion as well as the importance of the effect size.

Program budgeting and marginal analysis (PBMA) (Goodwin & Frew, 2013; Mitton & Donaldson, 2001; Mitton et al., 2003) explicitly considers the available budget and the budget impact of the decision options. Hence, the decision options are put into three categories: a) Funding growth areas with new resources, b) Decisions to move resources to areas with service growth, and c) Trade-off decisions to move resources. A deliberative discussion of decision-makers is based on these categories.

MAUT (Multi-attribute utility theory) (Shepard, 1964; Von Winterfeldt & Fischer, 1975; Yntema & Torgerson, 1961) translates the performance of options into utilities in different scenarios. Decision-makers estimate the probability of each scenario. The value of a specific option is calculated as the subjective expected utility (SEU), the sum of the utilities in all scenarios multiplied by the probability of each scenario. Afterwards, all options are compared regarding their SEU.

- **Outranking methods** do allow incomparability between the performances of different decision options. As such, low performance on one criterion cannot be outweighed by higher performance in another criterion.

ELECTRE (ELimination and Choice Expressing REality) (Crama & Hansen, 1983; Roy, 1968) aims to identify dominance relations between different options. For each criterion the dominant option will receive predefined weights, which represent the relative importance of the criterion. The option that outranks all other options should be selected.

PROMETHEE (Preference Ranking Organisation Method for Enrichment Evaluation) (Brans et al., 1986) is a method used to define preference functions. These preference functions describe a criterion's threshold of importance (e.g. 1 week of survival gain) as well as its gradient (e.g. the importance doubles if the survival gain is 4 weeks). Thereafter, outranking relationships between different options are calculated.

- **Reference based methods** compare the decision options with respect to an ideal alternative.

In goal programming (Charnes & Cooper, 1957; Charnes et al., 1955) the ideal performance on each decision criterion is defined as a goal. The differences between the goals desired and the performance of the real decision options are compared on all decision criteria. Accordingly, the best decision option is closest to the goal desired across all criteria.

TOPSIS (Technique for Order Preference by Similarity to Ideal Solution) describes a similar method to goal programming (Hwang & Yoon, 1981). For each criterion, the alternatives are compared regarding the distance from the Positive Ideal Solution (PIS) and the Negative Ideal Solution (NIS). The closeness coefficients that summarise the distance from PIS and NIS of each alternative are used to rank the alternatives.

- **Non compensatory MCDA methods** (Dodgson et al., 2009; Guitouni & Martel, 1998) differ from other MCDA methods as they do not allow trade-offs between different criteria. These methods use thresholds for different criteria, or apply lexicographical rankings to opt alternatives out.

Analytic approaches

- **Modeling methods** provide insights into the magnitude of an effect for new health technologies.

Modeling methods such as **decision trees** and **simulation approaches** (Rothman, 1941; Siebert, 2003; Stahl, 2008) can calculate quantitative outcomes such as costs and medical outcomes of health interventions. These methods require clear definitions of the health care pathway related to the technology of interest and data input to model the outcome at the end of the health care pathway.

The **efficiency frontier concept** (Caro et al., 2010; Koch, 2010) aims to integrate costs and effects of multiple interventions for specific outcome parameters. These parameters are plotted against the intervention costs in comparison to already existing interventions. The efficiency frontier thereby illustrates the gradient of improvement in outcomes versus the increase in costs.

Artificial neural networks (Basheer & Hajmeer, 2000; Rosas et al., 2013) are learning modeling systems and can be applied in a broad range of real-world problems. They can detect connections and patterns in data and adapt themselves accordingly.

- **Probability-based methods** provide insights into the likelihood of an effect for new health technologies.

Bayesian networks (Bayes & Prices, 1763; Pearl, 1985) describe a network consisting of nodes representing health care parameters. These nodes are interlinked by probability functions. Thresholds for specific outcome parameters define clinical relevance. The structure and the parameters of a Bayesian network (BNs) can be obtained from experts.

The Dempster–Shafer theory (DST) (Beynon et al., 2000; Dempster, 1967) is similar to the Bayesian approach. The evidence is decomposed into different statements and their plausibility in comparison to other statements. The outputs are statements with specific likelihoods.

Value of Information (VOI) analysis (Claxton et al., 2001; Howard, 1966) can clarify whether new data should be gathered. The expected value of perfect information (EVPI) is the willingness of decision-makers to pay for the uncertainty in the decision to be addressed. The expected value of partial perfect information (EVPPI) is the value difference between a decision based on perfect information on a subset of parameters and the current information.

Fuzzy logic (Grabisch, 1995; Murofushi & Sugeno, 1989; Murofushi & Sugeno, 1991; Zadeh, 1965) provides an intuitive way of scaling outcome parameters. Overlapping ranges describe the fuzziness of parameters. Experts can determine the fuzzy sets for parameters.

- **Qualitative modelling methods** illustrate the relation between all outcomes which contain qualitative and quantitative elements.

Logic models (Conrad et al., 1999; Wholey, 1987) allow the identification of patients, interventions, comparators, outcomes, context and implementation, thus providing a comprehensive and generic structure for the decision problem.

Reasoning mapping (Axelrod, 2015; Montibeller et al., 2008) is based on the decision-makers' reasoning of a decision problem. The decision problem is divided into different attributes. The context between attributes is illustrated as links of different strength (positive or negative) between attributes.

Preference elicitation approaches

DCEs (Discrete Choice experiments) (McFadden, 1976; McFadden, 1975) separate the decision criteria into different levels. Participants are asked to decide between two scenarios consisting of variations in criteria and levels. These ratings form the base for the calculation of preferences for every criterion and level.

Best-worst rating (BWS) (Finn & Louviere, 1992; Flynn et al., 2007; Potoglou et al., 2011; Yoo & Doiron, 2013) provide an alternative rating system. Participants have to rate the best and the worst criterion of each scenario. These ratings form the base for the calculation of preferences for every criterion and level.

Consensus methods

- **General consensus methods** are used for discussions of the final information (in this case the assessment results of the HTA) that informs the decision.

Consensus Reaching Processes (CRPs) (DeGroot, 1974; Eisenberg & Gale, 1959; Palomares et al., 2014) describe a variety of methods to measure the distances between different expert opinions or between individual and collective opinions. A feedback mechanism is intended to decrease these differences (numerical, intervals or linguistic).

The Delphi method (Dalkey & Helmer-Hirschberg, 1962) guides the decision panel on how to structure and to rate the decision problem according to e.g. alternatives, criteria, values and outcomes. Thereafter, the participants rate these aspects. These ratings form the basis for the discussion in the next Delphi round. This process should be repeated until consensus is reached.

Nominal group technique (NGT) (Allen et al., 2004; Delbecq & Van de Ven, 1971) is designed to include all participants in decision-making. Participants write down their individual viewpoints regarding a decision-problem. These viewpoints then form the basis for a discussion among the group. Through this discussion, different aspects of the decision problem can be finally ranked by the group.

A Citizens' jury (Crosby et al., 1986; Whitty et al., 2014a) comprises a random sample of the public who are involved in the decision-making. The citizens' jury provides a public viewpoint and ensures that the preferences and values of the public are included in the decision-making process.

- **Process-based consensus methods** are used for discussions during the assessment process that results in the final information for decision-making.

GRADE (Grading of Recommendations, Assessment, Development and Evaluation)/ Developing and Evaluating Communication Strategies to Support Informed Decisions and Practice Based on Evidence (DECIDE) (Atkins et al., 2004; Gopalakrishna et al., 2014; Guldbrandsson et al., 2015; Guyatt et al., 2008; Hsu et al., 2011; Treweek et al., 2013) aims at assessing the quality of evidence, the balance of desirable and undesirable consequences, values and preferences, and the use of resources. GRADE integrates the ratings on the quality of evidence (on a scale of 1 to 4) with ratings on the importance of certain outcomes (on a scale from 1 to 9) in a deliberative process. As GRADE does not inform users about how to take qualitative evidence such as context and implementation issues into account, it was developed further resulting in the tool DECIDE. DECIDE extends the list of criteria that are provided by GRADE and provides computer-based tools to comprehensively illustrate different criteria and the underlying evidence.

Realist synthesis (Pawson et al., 2004; Rycroft-Malone et al., 2012) describes an iterative process for systematic reviews. By doing this, the assessment methods can be adapted with respect to the specific decision context (such as the assessment of RCT or observational studies. The results should not only answer the question whether the intervention is working, but also why the intervention is working, and in which context. Finally, stakeholders can review the findings to provide useful recommendations.

Table 7: Relation between areas of application and approaches.

	Area of application	Overlaps with other area of application	Number of approaches assigned to the area of application
1	Structuring of the HTA into assessment criteria		16
2	Performance matrix of the assessment results	1	14
3	Qualitative modelling techniques to illustrate all relevant assessment aspects		2
4	Process based integration		2
5	Scoring and calculation techniques to integrate assessment criteria	1, 2	14
6	Providing structured input for deliberative discussions	2, 5	3
7	Structuring a deliberative discussion	5	4
8	Integrating uncertainty by using assessment criteria	5	6
9	Integrating uncertainty of evidence		6

assessment aspects (dimension 1) can be identified and addressed from before the application of the different assessment methods (such as overlaps between the assessment of context, implementation and the ethical and socio-cultural aspects). The selection process for the assessment criteria as well as the process of structuring the criteria should be guided by the objectives and values of decision makers (dimension 4). Thus, the dimensions 1 and the dimension 4 are integrated from the very beginning of HTA.

Technique 2: Performance matrix of the assessment results:

A performance matrix entails the graphical illustration of the assessment results (dimension 1) which is useful for structured qualitative decision-making, taking values and preferences of stakeholders (dimension 4) into account. Afterwards, this evidence is deliberated on in conjunction with additional criteria that are put forward by committee members (Coast, 2004). Based on a performance matrix, non-compensatory MCDA methods quantitatively compare different options by using different concepts: dominance; lexicographic ordering, or preselection via thresholds of certain criteria (or all criteria) (Dodgson et al., 2009). For instance, the performance matrix can lead to clear decisions if a particular technology dominates the performance in all assessment criteria.

Technique 3: Qualitative modelling techniques to illustrate all relevant assessment aspects:

Qualitative modelling techniques such as logic models represent a graphical illustration of context, implementation and interdependencies between different compounds of a technology. Logic models can be used to link and integrate different aspects of complex technologies (Anderson, 2011; Baxter et al., 2010). Reasoning mapping illustrates the context between different decision attributes, using arrows of different strength (positive or negative) between the respective attributes (Montibeller et al., 2008). The application of this modelling technique can illustrate the relation between all assessment aspects (dimension 1) and the modifying factors (dimension 2) in a comprehensive manner. For instance, specific patient characteristics (such as religious affiliation) can influence the outcome of palliative care with a specific compound of spiritual care. This way of presentation can increase the understanding of the interactions between the health care system and health technologies for HTA.

Technique 4: Process based integration to address interactions within the assessment:

This technique links the inputs (the evidence/outcome parameters to be assessed) and outputs (the assessment results) regarding the different interacting assessment aspects. The output of one assessment aspect can be the input for the assessment of another aspect. For instance, assessment results on modifying factors (dimension 2) such as patient preferences for death at home can feed as an outcome parameter into the assessment of effectiveness (dimension 1) to assess if reinforced palliative care helps patients die at home. Stakeholders can be involved and contribute their perspectives (dimension 4) throughout different steps of the assessment process. The GRADE methodology also covers some aspects of process-based integration: GRADE guides a process from the evidence synthesis to the decision-making process. A panel formulates the research question according to the PICO (Participants, Intervention, Comparator, Outcomes) scheme and rates the importance of certain outcomes. Finally, the results of the evidence synthesis are discussed according to pre-defined criteria.

Technique 5: Scoring and calculation approaches to integrate assessment criteria:

These techniques are classified under MCDA approaches to systematically integrate the assessment results (dimension 1, 2 and 3) and values of preferences of stakeholders (dimension 4). For instance, the application of MCDA in the case study on palliative care could quantitatively indicate that the evidence on effectiveness for caregivers contributed with 59% to the overall value of reinforced models of care for participating stakeholders. As outlined in the description of MCDA approaches in the appendix, there are various MCDA methods available.

Technique 6: Providing structured input for deliberative discussions:

There is a large variety of structured inputs available for a deliberative discussion between stakeholders and decision makers (dimension 4). For instance, EVIDEM developed a contextual tool for non-quantifiable criteria. Using the tool, all qualitative criteria are assessed whether they have a positive, negative or neutral influence on the decision. The final discussion is then based on this rating. The final discussion using GRADE is structured according to four criteria: quality of evidence, balance benefits/harm; the value and preference and resource use (costs).

Technique 7: Structuring a deliberative discussion:

Several approaches to structure a deliberative discussion were identified to reinforce the input of all participating stakeholders (dimension 4). For instance, by applying Nominal group technique (NGT), participants write down their individual viewpoints regarding a decision problem. These viewpoints then form the basis for the discussion among the group. Through this discussion, different aspects of the decision problem can be finally ranked by the group.

Technique 8: Integrating uncertainty by using assessment criteria:

Uncertainty of evidence can be addressed by using specific assessment criteria for uncertainty. For instance, GRADE and EVIDEM consider the validity and consistency of evidence as separate assessment criteria. Preferences of stakeholders can indicate the importance of these criteria according to technique 6. Uncertainty can also be considered in the scaling system of other assessment criteria (e.g. by providing ranges of scores for assessment criteria). For instance, the evidence can indicate a pivotal effect regarding quality of life for reinforced models of palliative care. As the uncertainty around the study quality was high, stakeholders could rate the effect including the uncertainty surrounding this effect with a range from +2 to +5 on a scale from 0 (no effect) to 5 (substantial effect). In this way, uncertainty (dimension 3) and the preferences and perspectives of decision makers (dimension 4) can be brought together.

Technique 9: Integrating uncertainty of evidence:

Evidence on different assessment aspects (e.g. the outcome of reinforced palliative home care on patients' quality of life and the assessment results on patient moderators regarding quality of life) can be processed to obtain integrated information about the probability for an effect regarding quality of life for specific patients. Consequently, this technique provides integrated information on assessment results (dimension 1), modifying factors (dimension 2) and uncertainty surrounding the results (dimension 3). Analytic methods such as decision trees (Cooper et al., 2005) or simulation approaches (Arunraj et al., 2013) provide these outputs. Bayesian networks are especially useful for illustrating uncertainty in complex systems. The Bayesian networks can be constantly updated when new evidence comes in (Stewart et al., 2014; Woertman et al., 2014), which is similar to the approach of the Dempster–Shafer theory (DST).

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Table 8: Included methods according to the four dimensions of information in HTA.

Approach	Dimensions to be integrated: Addressed by certain approaches					
	Evidence related dimensions (dimensions 1,2 and 3)			Representation of stakeholders with their values and preferences (dimension 4)		
	Dimension 1: Different assessment aspects of a technology, such as medical outcomes, legal issues or economic outcomes	Dimension 2: Modifying factors, such as patient characteristics, context and implementation	Dimension 3: Degree of uncertainty, such as validity of evidence	Values and preferences for assessment results: effectiveness, economics ethics, socio-cultural, legal issues	Perception and understanding	Consensus for HTA recommendation (feasibility and values)
AHP (Analytic hierarchy process) (Hummel et al., 2012; Liberatore & Nydick, 2008)	/	Hierarchical structure of criteria	/	Pairwise comparison of criteria using a scale from 9 to 1/9	/	Calculation of an inconsistency ratio
Analytic approaches (e.g. decision trees (Cooper et al., 2005), simulation approaches (Arunraj et al., 2013))	/	Context illustrated in model structure	Sensitivity analysis, variation of parameters, face validation to assess robustness of model	Can show links between different criteria	/	Comparison to alternative interventions possible
ANP (Analytic Network process) (Liao & Chang, 2009; Saaty, 2004)	/	Network structure	/	Pairwise comparison of criteria using a scale from 9 to 1/9	/	Decision between several alternatives
Artificial neural networks (Basheer & Hajmeer, 2000; Rosas et al., 2013)	Processing of several parameters	Weighting of different parameters regarding their contribution to a certain output	Feedback mechanism to improve network system and reduce validation error	/	/	/
Bayesian analyses (Stewart et al., 2014; Woertman et al., 2014)	/ (can only synthesize same outcome parameter including likelihood to reach clinical relevant threshold)	Bayesian network consisting of nodes which are interlinked by probability functions.	Uncertainty is illustrated in the 95% confidence interval (contrast to frequent statistics) considered by bias terms	The structure and the parameters of a Bayesian network (BNs) can be obtained from evidence and stakeholders	95 % probability means that the true parameter lies within this interval; can state whether a clinically relevant outcome is likely	Comparison between multiple interventions possible

Best-worst rating (BWS) (Flynn et al., 2007; Potoglou et al., 2011; Yoo & Doiron, 2013)	Regression analysis of scenarios for every criterion and level	/	/	Responders are asked to rate the best and the worst criterion of a single scenario; finally preferences for different outcomes are calculated using regression analysis	/	Can compare multiple alternatives
Citizens' jury (Whitty et al., 2014a)	/	/	/	Random sample of public should cover the diverse preferences and values of publics	Experts give advice to citizens' jury about the decision problem	Random sample of citizens provides an unbiased public viewpoint; this viewpoint can result in a consensus or a recommendation to decision-makers
Consensus Reaching Processes (CRPs) (Palomares et al., 2014)	/			Assessments represented as numerical, intervals or linguistic parameters.		The distances between different expert ratings or between individual and collective ratings are essential for integration. A feedback mechanism is intended to decrease these differences (numerical, intervals or linguistic).
DCE (Discrete Choice Experiment) (Hoefman et al., 2014; Johnson et al., 2014; Klojgaard et al., 2014; Seghieri et al., 2014; Whitty et al., 2014b)	Regression analysis of scenarios for every criterion and level	/	/	Hypothetical trade-off decisions for different scenarios (for every criterion and level, calculation by regression analysis)	/	Option to compare different alternatives
Delphi method (Back-Pettersson et al., 2008; Berra et al., 2010; Hawkins et al., 2006)	/	/	/	Panel of experts defines decision problem e.g. reimbursement decision; opportunity to structure and rate the decision problem according to e.g. alternatives, criteria, values and outcome dimensions	/	The results of the panel will be reassessed in the following Delphi rounds
Efficiency frontier concept (Koch, 2010)	Quantitative parameters are plotted against the intervention costs	/	/	/	/	The efficiency frontier describes a favorable cost to benefit relation in comparison to already existing interventions

Approach	Dimensions to be integrated: Addressed by certain approaches					
	Evidence related dimensions (dimensions 1,2 and 3)			Representation of stakeholders with their values and preferences (dimension 4)		
	Dimension 1: Different assessment aspects of a technology, such as medical outcomes, legal issues or economic outcomes	Dimension 2: Modifying factors, such as patient characteristics, context and implementation	Dimension 3: Degree of uncertainty, such as validity of evidence	Values and preferences for assessment results: effectiveness, economics ethics, socio-cultural, legal issues	Perception and understanding	Consensus for HTA recommendation (feasibility and values)
ELECTRE (ELimination and Choice Expressing REality) (Carrico et al., 2012; Cheng et al., 2002)	Indifference thresholds for clear dominant relations are defined	/	/	For each criterion, the dominant option will receive predefined weights, which represent the relative importance of a criterion Clear outranking relations between different options.	Provides multiple opportunities for decision-makers to refine the model	Calculation of concordance/ disconcordance indices. These basically consist of the weights of all dominant criteria of an alternative divided by the sum of all weights.
EVIDEM (Evidence based decision-making)	Direct weighting on a scale of 1 to 5	/	Direct weighting on a scale of 1 to 5 as one criterion (validity of evidence)	Direct weighting on a scale of 1 to 5	/	Final deliberative discussion
Evidence theory or Dempster–Shafer theory (DST) (Bell, 2005)	/	/	Combines different pieces of evidence and their plausibility of the evidence to come to statements with certain probabilities	/	/	/
Fuzzy logic (Grabisch & Labreuche, 2005)	Outcomes can be rated as over-lapping fuzzy regions	/	/	Stakeholder can determine the fuzzy sets for criteria	/	/
Goal programming (Aouni & Kettani, 2001)	/	/	/	Calculation of deviation between goals and criterion values for certain alternatives	/	Definition of desirable goals for each criterion by decision-makers

GRADE (Grading of Recommendations Assessment, Development and Evaluation) (Gopalakrishna et al., 2014; Guyatt et al., 2008; Hsu et al., 2011) DECIDE (Developing and Evaluating Communication Strategies to Support Informed Decisions and Practice Based on Evidence) Guldbrandsson et al., 2015)	Part of quality assessment and deliberative discussion	/	Methodological assessment of quality on a 4 point scale	Panel formulates research question according to PICO and determines the importance of each outcome on a scale of 1 (not important) to 9 (critical)	/	Deliberative discussion of a decision committee; Decision is made according to the criteria: quality of evidence, balance benefits/harms; the value and preference and resource use (costs); two grades for strength of recommendations
Logic models (Anderson, 2011; Baxter et al., 2010)	/	Can integrate the interdependencies between outcomes and context	/	/	Logic models can improve the understanding of complex interventions	/
MACBETH (Measuring Attractiveness by a Category Based Evaluation Technique) (Santos et al., 2013)	/	/	/	Pairwise comparison between 2 criteria on a scale from 1 to 6	/	Calculation of a consistency ratio
MAUT (Multi-attribute utility theory) (Brink, 1994)	/	/	Decision-makers need to judge the likelihood for different scenarios	Outcomes are translated into preference scores to calculate utilities (common unit for all effects) for different scenarios with different likelihoods	/	Value of technologies is calculated by the subjective expected utility (SEU): sum of all utilities in all scenarios for each technology
Nominal group technique (NGT) (Allen et al., 2004)	/	/	/	Participants write down their ratings regarding a certain decision problem.	Ideas are shared among the group, discussed, modified and finally voted and ranked.	Ideas are shared among the group, discussed, modified and finally voted and ranked.
Non compensatory MCDA methods (Dodgson et al., 2009)	/	/	/	Different concepts: dominance, lexicographic ordering, preselection via thresholds in certain criteria (one or each criterion) or mixed process	/	Judgments about importance of criteria by defining thresholds for benchmarking

Approach	Dimensions to be integrated: Addressed by certain approaches					
	Evidence related dimensions (dimensions 1,2 and 3)			Representation of stakeholders with their values and preferences (dimension 4)		
	Dimension 1: Different assessment aspects of a technology, such as medical outcomes, legal issues or economic outcomes	Dimension 2: Modifying factors, such as patient characteristics, context and implementation	Dimension 3: Degree of uncertainty, such as validity of evidence	Values and preferences for assessment results: effectiveness, economics ethics, socio-cultural, legal issues	Perception and understanding	Consensus for HTA recommendation (feasibility and values)
Programme budgeting and marginal analysis (PBMA) (Goodwin & Frew, 2013; Mitton et al., 2003)	Scoring of decision criteria	/	/	Definition of locally relevant decision making criteria	/	Additional deliberative discussion of decision committee and validity check with external stakeholders: a) Funding growth areas with new resources b) Decisions to move resources to areas with service growth c)Trade-off decisions to move resources
PROMETHEE (Preference Ranking Organisation Method for Enrichment Evaluation) (Frikha, 2014; Mavrotas et al., 2006)	Preference function and weighting	/	/	Free choice of methods e.g. point allocation	/	Performing outranking relationships between alternatives
Realist synthesis (Rycroft-Malone et al., 2012)	/	/	/	/	Result does not only explain if an intervention works, but also why	Combines evidence search and stakeholder values; stakeholder are involved throughout the evidence search and synthesis process to come up with a result
Reasoning mapping (Montibeller et al., 2008)	Ordinal scaling of criteria	The context between different criteria is illustrated trough links of different strength (positive or negative) between attributes	/	Building of a Reasoning Map for problem- structuring: capturing a decision maker's reasoning as a network of means and ends concepts.	Decision maker's reasoning essential part of the reasoning map	Can be used to assess several alternative options

REMBRANDT (Ratio Estimation in Magnitudes or deci-Bells to Rate Alternatives which are Non-DominaTed) (Lootsma, 1992)	/	/	/	Pair wise comparison between 2 criteria on a scale from -8 to +8 (direct rating system on a logarithmic scale)	/	Calculation of an inconsistency ratio
Swing weighting method (Belton & Stewart, 2002) and SMARTS (Simple Multi-Attribute Rating Technique Using Swings (Edwards & Barron, 1994b)	The swing weighting method reflects both, the importance of a criterion.	/	/	The swing weighting method reflects both the importance of a criterion as well as the importance of the effect size.	/	/
TOPSIS (Technique for Order Preference by Similarity to Ideal Solution) (Hwang & Yoon, 1981)	Calculate the distance of each alternative from PIS and NIS	/	/	/	/	Determination of the Positive Ideal Solution (PIS) and Negative Ideal Solution (NIS) for each criteria Calculation of the closeness coefficient of each alternative to rank alternatives
Value of Information (VOI) analysis (Corro Ramos et al., 2013)	The EVPPI can identify on which parameters additional data should be collected regarding the expected value and costs	/	The expected value of partial perfect information is the EVPPI, the value difference between a decision based on perfect information on a subset of parameters and current information	The expected value of perfect information (EVPI) is the willingness of decision makers to pay for the uncertainty in the decision to be resolved	/	/ /

Table 9: Integrative techniques of included approaches.

Approaches	The separation of a decision into criteria	Structuring criteria	Performance matrix	Qualitative modelling techniques	Process based integration	Scoring and calculation approaches to integrate criteria	Techniques as input for deliberative discussions	Techniques for structured deliberative discussions	Preferences and criteria to integrate uncertainty	Quantitative modelling techniques to address uncertainty of evidence
AHP (Hummel et al., 2012; Liberatore & Nydick, 2008)	X	X	X			X		X		
ANP (Liao & Chang, 2009; Saaty, 2004)	X	X	X			X				
Analytic approaches such as decision trees (Cooper et al., 2005), simulation approaches (Arunraj et al., 2013)										X
Artificial neural networks (Basheer & Hajmeer, 2000; Rosas et al., 2013)										X
Bayesian analyses (Stewart et al., 2014; Woertman et al., 2014)										X
BWS (Flynn et al., 2007; Potoglou et al., 2011; Yoo & Doiron, 2013)	X		X			X				
Citizens' jury (Whitty et al., 2014a)								X		
Consensus methods (Palomares et al., 2014)								X		
DCE (Hoefman et al., 2014; Johnson et al., 2014; Klojgaard et al., 2014; Seghieri et al., 2014; Whitty et al., 2014b)	X		X			X				
Delphi method (Back-Pettersson et al., 2008; Berra et al., 2010; Hawkins et al., 2006)								X		
Efficiency frontier concept (Koch, 2010)										X
ELECTRE (Carrico et al., 2012; Cheng et al., 2002)	X		X			X				
EVIDEM (Goetghebeur et al., 2012; Goetghebeur et al., 2010; Miot et al., 2012; Tony et al., 2011)	X	X	X			X	X		X	

Evidence theory or DST (Bell, 2005)										X
Fuzzy logic (Grabisch & Labreuche, 2005)	X								X	
Goal programming (Aouni & Kettani, 2001)	X		X			X				
GRADE/DECIDE (Gopalakrishna et al., 2014; Guldbrandsson et al., 2015; Guyatt et al., 2008; Hsu et al., 2011)	X				X	X	X		X	X
Logic models (Anderson, 2011; Baxter et al., 2010)				X						
MAUT (Brink, 1994)		X				X			X	
MACBETH (Santos et al., 2013)	X		X			X				
NGT (Allen et al., 2004)								X		
Non compensatory MCDA methods (Dodgson et al., 2009)	X		X							
PBMA (Goodwin & Frew, 2013; Mitton et al., 2003)	X		X				X			
PROMETHEE (Frikha, 2014; Mavrotas et al., 2006)	X		X			X			X	
Realist synthesis (Rycroft-Malone et al., 2012)					X					
Reasoning mapping (Montibeller et al., 2008)				X						
REMBRANDT (Lootsma, 1992)	X		X			X				
Swing weighting method (Belton & Stewart, 2002)	X		X			X				
TOPSIS (Hwang & Yoon, 1981)	X		X			X				
VOI analysis (Corro Ramos et al., 2013)									X	
Reported techniques	**16**	**4**	**14**	**2**	**1**	**14**	**3**	**4**	**6**	**5**

1 Integrated health technology assessment for evaluating complex technologies (INTEGRATE-HTA): An introduction to the guidances

3 Guidance for assessing effectiveness, economic aspects, ethical aspects, socio-cultural aspects and legal aspects in complex technologies

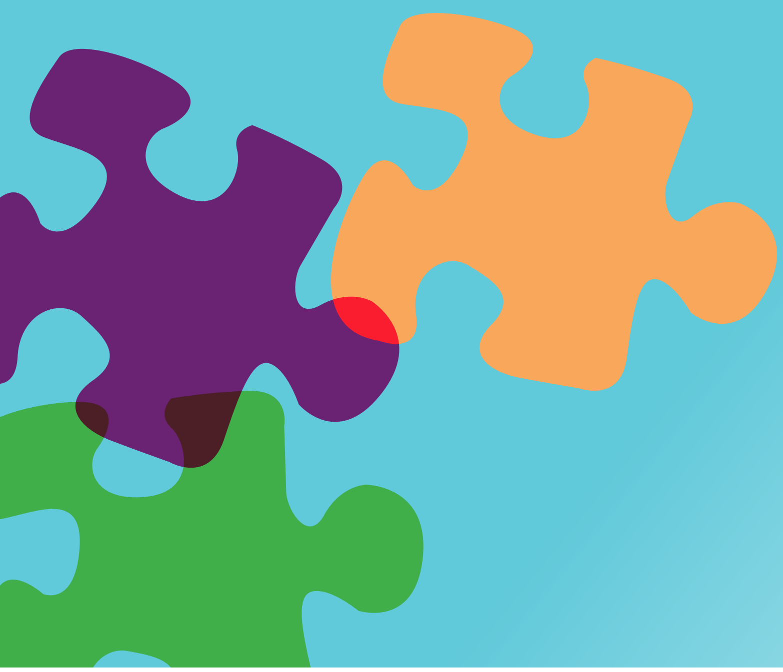
4 Guidance for the assessment of treatment moderation and patients' preferences

5 Guidance for the Assessment of Context and Implementation in Health Technology Assessments (HTA) and Systematic Reviews of Complex Interventions: The Context and Implementation of Complex Interventions (CICI) Framework

6 Guidance on the use of logic models in health technology assessments of complex interventions

7 Guidance on choosing qualitative evidence synthesis methods for use in health technology assessments of complex intervention

8 Integrated assessment of home based palliative care with and without reinforced caregiver support: A demonstration of INTEGRATE-HTA methodological guidances – Executive Summary



INTEGRATE-HTA

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