

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

3

***EDITORS:** Kristin Bakke Lysdahl, Kati Mozygemba, Jacob Burns, James B. Chilcott, Jan Benedikt Brönneke, Bjørn Hofmann*

INTEGRATE-HTA



This project is co-funded by the European Union under the Seventh Framework Programme (Grant Agreement No. 306141)

PLEASE CITE THIS PUBLICATION AS:

LYSDAHL, K.B., MOZYGEMBA, K., BURNS, J., CHILCOTT, J.B., BRÖNNEKE, J.B., HOFMANN, B. (eds.) (2016) *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/>

CONTACT:

For questions regarding this document, contact INTEGRATE-HTA (info@integrate-hta.eu)

DATE:

Version of 01/02/2016

PROJECT:

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

COORDINATOR:



PARTNER:



The research leading to these results has received funding from the European Union Seventh Framework Programme ([FP7/2007-2013] [FP7/2007-2011]) under Grant Agreement No. 306141.

DISCLAIMER:

The sole responsibility for the content of this publication lies with the authors. It does not necessarily reflect the opinion of the European Union. The European Commission is not responsible for any use that may be made of the information contained therein.

About this guidance



Who would find this guidance useful?

This guidance is useful for health technology assessment (HTA) researchers and other stakeholders engaged in the assessment of health technologies, stakeholders using and planning to use HTAs, and the interested public.

Purpose and scope of this guidance

The purpose of this guidance is to facilitate the assessment of complex health technologies, by providing concepts, frameworks, approaches, and methods for assessing the effectiveness, as well as economic, ethical, socio-cultural and legal aspects in the context of HTA.

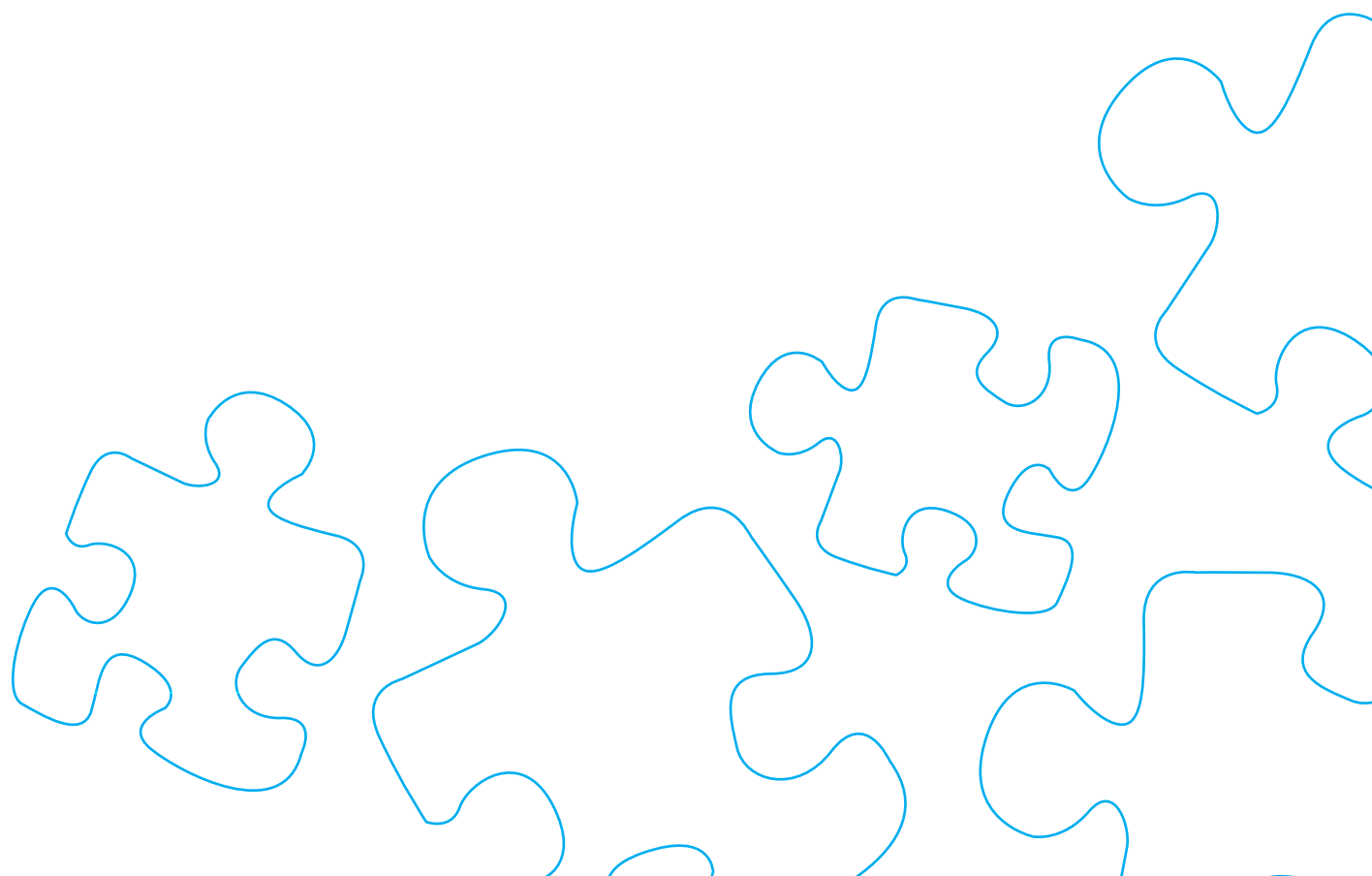
Added value for integration / complex technologies

The guidance is directed towards some of the specific challenges when assessing complex health technologies, such as heterogeneous study designs, multiple stakeholder perspectives, and unpredictable outcomes. It provides solutions to some of these challenges by complementing, expanding on, and adding new methods to the existing resources.

INTEGRATE-HTA

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

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



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 context-dependent - current HTA usually focusses on the technology, not on the system within it is used,
- ▶ perform differently depending on the way they are implemented,
- ▶ have different effects on different individuals,
- ▶ are complex.

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. They have been described in six guidances.

This guidance deals with some of the specific challenges when assessing complex health technologies, such as heterogeneous study designs, multiple stakeholder perspectives, and unpredictable outcomes.

Purpose and scope of the guidance

The purpose of this guidance is to facilitate health technology assessment (HTA) of complex health technologies. HTA of complex health technologies, such as disease management programs, lifestyle intervention and therapies for people with chronic or multiple morbidities, is challenging due to a high level of uncertainty and unpredictability involved. All technologies are to some degree complex and therefore aspects of this guidance may also have more generic relevance. The complexity of a health technology may be difficult to determine when preparing the HTA. This guidance describes how the complexity of a health technology can be assessed, which can be applied to a broad range of technologies.

The guidance comprises five interlinked aspects of HTA: effectiveness, economic, socio-cultural, ethical and legal aspects, which altogether provide concepts, methods, approaches and frameworks for handling the challenges of assessing complex health technologies. The guidance evaluates the appropriateness of existing methodological approaches, and provides guidance for the selection and further development of these approaches. In addition new methodological tools are developed, particularly for the socio-cultural and the legal assessment aspects, where the methodological guidance available has so far been scarce.

Development of the guidance

The development of the guidance differs between the five aspects of HTA included in this guidance, as this relates to the nature of the field. One common feature is that the development draws on existing and published knowledge in the fields of HTA, complexity science, as well as knowledge of research methodologies in the five respective fields (effectiveness, economics, ethics, socio-cultural theory, and law). All guidance parts were informed by stakeholder involvement. This is a second common feature of all parts of the guidance. The concepts and methods suggested in the different guidance parts have been applied and modified through application to demonstration in the case study on reinforced home based palliative care, and adjusted due to collaboration and feedback between the researchers in the project. Finally, the guidance has been revised after valuable feedback from internal and external reviewers.

Application of the guidance

For a comprehensive integrated assessment of a complex technology we have 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. A system-based logic model is developed in Step 2. It provides a structured overview of technology, the context, implementation issues, and relevant patient groups. This informs the assessment of the effectiveness, as well as economic, ethical, legal, and socio-cultural aspects in Step 3, i.e. the aspects included in this guidance. 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).

The parts of this guidance, focusing on effectiveness, as well as economic, ethical, socio-cultural and legal aspects, could be used separately (i.e., to assess one particular aspect of a complex health technology). However, it is strongly recommended to address the different parts in a comprehensive and integrated HTA. The main components in applying of the different parts of the guidance are as follows:

The **effectiveness guidance** gives an overview of existing methods and provides guidance for dealing with heterogeneous study designs in effectiveness reviews of complex interventions, and summarizes existing methods and provides guidance for evidence synthesis in effectiveness reviews of complex interventions. Which of the highlighted methods are appropriate depends on the effectiveness research question, the specific technology and the system within which it exists, the resulting complexity, and the available evidence base. This guidance highlights the aspects that should be considered when making these decisions and outlines the implications of such considerations in selecting methods. Choosing appropriate types of evidence and methods for evidence synthesis should ensure that decision makers are provided with appropriate information to inform the decision making process.

The **economics guidance** aims to identify the potential impact of complexity for health economic evaluations within HTA. A review of health economics guidance relating to HTA was undertaken with a focus on its relevance and appropriateness for the evaluation of complex interventions acting in complex settings. Guidance recommendations were developed from the review, tested and further developed through implementation in a demonstration economics case study in reinforced care giver support in home palliative care. Guidance includes recommendations for practice, focusing on systems approaches to model based health economic evaluation for complex interventions in complex settings and recommendations for methodological research.

The **ethics guidance** provides a stepwise procedure for addressing ethical aspects in the assessment of HTA, with the following main content elements: A) Assessing the complexity of the technology, using the characteristics of complexity relevant for ethical analyses, such as Multiple and changing perspectives, Indeterminate phenomena, Uncertain causality, Unpredictable outcomes, and Ethical complexity. B) Finding the best type of ethical approach to use for this type of complex technology (based on A), selecting amongst existing available approaches for ethical assessment. Tools for the selections are provided, which take into account contextual factor of the HTA commissioners, in addition to the complexity profile of the technology. C) Guiding how

to adjust existing ethical methods for assessing complex interventions, based on information about general features of the ethical approaches, and on information about important ethical aspect of the specific technology. D) Providing guidance on how to apply the ethical approach, emphasizing integration perspectives. How the context of the health technology and the HTA influences the main steps in ethical analyses in the framework is outlined.

The **socio-cultural guidance** presents a framework for the identification and evaluation of socio-cultural aspects relevant in HTA as well as a stepwise assessment process. The socio-cultural framework contains three main categories – the socio-cultural understanding of the health issue, the understanding of the health technology and socio-cultural aspects of the implementation of the technology. These three categories summarize eight sub-categories. The framework can be applied on each step of the suggested assessment process, i.e. to identify and to evaluate socio-cultural aspects of health technologies as well as to structure the results of the assessment. The guidance offers four methodological approaches, presented with advantages and disadvantages. Furthermore, theoretical approaches are taken into account, which can help structuring the whole HTA and/or the understanding of specific aspects of the socio-cultural assessment. We also refer to theoretical approaches as an option to capture cultural heterogeneity of different social groups using Cultural Theory as an example.

The **legal guidance** provides a structured framework to allow HTA conductors without legal education to identify legal aspects relevant for the assessment of complex health technologies and, with that, to allow for a better integration of legal aspects in HTA of such technologies. The guidance focuses on nine core aspects, which are potentially relevant. The guidance allows focusing on legal aspects that are of major importance for the specific HTA by pointing out relations between each core aspect and other (also non-legal) aspects of the HTA as well as the respective relevant level of decision-making. Determining these connections allows the user of this guidance to avoid unnecessary assessments of legal aspects of minor relevance for the specific HTA.

Conclusions/added value

This guidance is directed towards some core challenges when assessing complex health technologies, such as heterogeneous study designs, multiple stakeholder perspectives, and unpredictable outcomes. It provides solutions to some of these challenges by complementing, expanding on, and adding new methods to existing resources, for assessing the effectiveness, as well as economic, ethical, socio-cultural, and legal aspects in HTA.

List of abbreviations

AHTAPoI	Agency for Health Technology Assessment Poland
AIMD	Active Implantable Medical Devices
ASERNIP-S	Australian Safety and Efficacy Register of New Interventional Procedures–Surgical
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
CADTH	Canadian Agency for Drugs and Technologies in Healthcare
CBA	Cost Benefit Analysis
CC	Cochrane Collaboration
CCA	Cost Consequence Analysis
CCOHTA	Canadian Coordinating Office for Health Technology Assessment
CE	Conformité Européene
CEA	Cost-Effectiveness Analysis
CFR	Charter of Fundamental Rights
CHMP	Committee for Human Medicinal Products
CI	Cochlear implant
CMA	Cost-Minimization Analysis
CMDh	Co-ordination group for Mutual recognition and Decentralised procedures–human
CMS	Concerned Member States
CTA	Constructive Technology Assessment
CUA	Cost Utility Analysis
CVA	Cost-Value Analysis
CVD	Cardiovascular disease
DACETHA	Danish Centre for Technology Assessment
DAHTA @DIMDI	German Agency for HTA at the German Institute for Medical Documentation and Information
DCP	Decentralised Procedure
GVS	Drug Reimbursement System
EC	European Commission
ECHR	European Convention on Human Rights
EEC	European Economic Community
ELSI	Ethical, Legal and Social Implications
EMA	European Medicines Agency
EPC	European Patent Convention
EPO	European Patent Office
EPOC	Effective Practice and Organisation of Care
EU	European Union
EUnetHTA	European Network for Health Technology Assessment
G-BA	Federal Joint Committee
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMC	General Medical Council
GP	General practitioners
HAS	Haute Autorité de Santé
HBPC	Home-based palliative care
HIQA	Health Information and Quality Authority
HIS	Healthcare Improvement Scotland
HTA	Health Technology Assessment

ICER	Incremental cost-effectiveness ratio
ICESCR	International Covenant on Economic, Social and Cultural Rights
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
iHTA	Interactive Health Technology Assessment
IMP	Investigational medicinal products
INAHTA	International Network of Agencies for Health Technology Assessment
IQWiG	Institute for Quality and Efficiency in Healthcare
ISPOR	International Society for Outcomes Research
IQWiG	Institute for Quality and Efficiency in Healthcare
ITS	Interrupted time series
IVDD	In Vitro Diagnostic Medical Devices
LBI-HTA	Ludwig Boltzmann Institute for Health Technology Assessment
MA	Meta-analysis
MAST	Model for Assessment of Telemedicine Applications
MDD	Medical device directive
MHRA	Medicines and Healthcare Products Regulatory Agency
MRC	Medical Research Council
MRP	Mutual Recognition Procedure
NHC	New Zealand National Health Committee
NHMRC	National Health and Medical Research Council
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NOMA	Norwegian Medicines Agency
NRS	Nonrandomized studies
OECD	Organisation for Economic Co-operation and Development
OTA	Office of Technology Assessment
PC	Palliative care
PH	Public Health
PICO	Patient-Intervention-Comparison-Outcome
PSM	Problem Structuring Methods
QALY	Quality Adjusted Life Years
QoL	Quality of Life
RCT	Randomized controlled trial
rHBC	reinforced Home-Based Palliative Care
RMS	Reference Member State
SAP	Stakeholder Advisory Panel
SBU	Statens Beredning För Medicinsk Utvärdering
SODA	Strategic Options Decision Analysis
SR	Systematic review
SSM	Soft Systems Methodology
SST	Social Shaping of Technology
TAW	Topic Advisory Workshop
TFEU	Treaty on the Functioning of the European Union
UDHR	Universal Declaration of Human Rights
WHO	World Health Organization
WMA	World Medical Association
WRE	Wide Reflective Equilibrium
WTP	Willingness to pay

Table of contents

	List of Tables	12
	List of Figures	13
1	INTRODUCTION	15
1.1	Purpose and scope of the guidance	15
1.1.1	Aim of this guidance	15
1.1.2	Target audience for this guidance	15
1.1.3	The added value of this guidance in relation to existing guidance	15
1.1.4	How this guidance relates to an integrated assessment process	16
1.2	Background	16
1.2.1	Complexity	16
1.3	Guidance development	18
1.4	Application of the Guidance	18
1.4.1	Interrelationships between the five aspects of the guidance	18
2	GUIDANCE TO ASSESS EFFECTIVENESS ASPECTS	20
2.1.1	Purpose and scope of the guidance	20
2.1.2	Background	21
2.1.3	Complexity and integration perspectives	23
2.2	Guidance development	24
2.2.1	Series of journal articles, focusing on methodological developments in systematic reviews of effectiveness	24
2.2.2	Other INTEGRATE-HTA guidances	24
2.2.3	Effectiveness reviews of complex technologies	24
2.3	How to apply the guidance	27
2.3.1	Conducting a comprehensive scope of the assessment	28
2.3.2	Gaining a thorough understanding of the characteristics of available methods	29
2.3.3	(Conditionally) specifying methods a priori	35
2.3.4	Assessing of methodological and clinical heterogeneity	37
2.3.5	Specifying final decision on methods	38
2.4	Conclusion	38
2.4.1	Main insights for the assessment of complex technologies	38
3	GUIDANCE TO ASSESS ECONOMIC ASPECTS	41
3.1	Introduction	41
3.1.1	Purpose and scope of the guidance	41
3.1.2	Background	41
3.2	Guidance development	42
3.2.1	Process of guidance development	42
3.2.2	Review of existing guidance on economic evaluation within HTA	42
3.2.3	Conclusions of the review of existing economic guidance within HTA	42
3.3	How to apply the guidance	43
3.3.1	Guidance recommendations for methodological research and practice in the economic evaluation of complex interventions in complex settings	43
3.3.2	Applying the recommendations for practice: A systems approach for development of health economic models for complex interventions in complex settings	46
3.4	Conclusion	58
3.4.1	Main insights for the integrated assessment of complex technologies	58
3.4.2	Strengths and limitations of current methods	59
3.4.3	Outlook	59
4	GUIDANCE TO ASSESS ETHICAL ASPECTS	60
4.1	Introduction	60
4.1.1	Purpose and scope of the guidance	60
4.1.2	Background	60
4.1.3	Complexity and integration perspectives	61
4.1.4	Available ethical approaches	65
4.2	Guidance development	65
4.3	How to apply the guidance	66

4.3.1	Assessing complexity of the technology (step 1)	66
4.3.2	Selecting ethical approach (step 2)	67
4.3.3	Confirming and modifying ethical approach (step 3)	69
4.3.4	Applying the ethical approach (step 4)	73
4.3.5	Outcome of ethical assessment (step 5)	75
4.4	Conclusion	75
4.4.1	Main insights for the assessment of complex technologies	75
4.4.2	Strengths and limitations of current approach(s)	75
4.4.3	Outlook	75
5	GUIDANCE TO ASSESS SOCIO-CULTURAL ASPECTS	76
5.1	Introduction	76
5.1.1	Purpose and scope of the guidance	76
5.1.2	Background	76
5.1.3	Description of available approaches to address socio-cultural aspects in HTA	79
5.1.4	Complexity and integrative perspective	82
5.2	Guidance development	82
5.3	How to apply the guidance	96
5.3.1	Assessment step 1: Assess the complexity of the intervention	97
5.3.2	Assessment step 2: Identify and prioritize relevant aspects and stakeholders	97
5.3.3	Assessment step 3: Validate the identified aspects	99
5.3.4	Assessment step 4: Assess prioritized aspects in more detail	99
5.3.5	Assessment step 5: Present the evidence	100
5.4	Conclusion	100
5.4.1	Main insights	100
5.4.2	Strengths and limitations of the current method	100
5.4.3	Outlook	100
6	GUIDANCE TO ASSESS LEGAL ASPECTS	101
6.1	Introduction	101
6.1.1	Purpose and scope of the guidance	101
6.1.2	Background	101
6.1.3	Existing approaches to address legal aspects in HTA	101
6.2	Guidance development	103
6.3	Application of guidance on identification of legal aspects in HTA	103
6.3.1	Determining relevant decision level (Step 1)	104
6.3.2	Determining specific relevant legal aspects (Step 2)	105
6.3.3	In-depth assessment of identified aspects (Step 3)	105
6.3.4	Nine Core Issues	105
6.4	Conclusion	112
6.4.1	Main insights	112
6.4.2	Strengths and limitations of current method	112
6.4.3	Outlook	112
7	ACKNOWLEDGEMENT	113
8	REFERENCES	114
9	APPENDIX	125
9.1	Appendix of the assessment of economic aspects in HTA	125
9.1.1	Review of existing guidance on economic evaluation within HTA	125
9.1.2	Theoretical underpinning, health economics methodology and perspective	125
9.1.3	Scoping and defining the economic decision problem	129
9.1.4	Health and wellbeing outcomes	133
9.1.5	Resources and costs	136
9.1.6	Conclusions of the review of existing economic guidance within HTA	139
9.1.7	References	140
9.2	APPENDIX OF THE ASSESSMENT OF SOCIO-CULTURAL ASPECTS IN HTA	143
9.2.1	Literature review on methods to assess socio-cultural aspects of health technologies	143
9.2.2	Overview of INAHTA-agencies that addressed socio-cultural aspects in HTA	144
9.2.3	Cultural Theory as an example of a theoretical approach to address heterogeneity in HTA	145
9.2.4	Framework categories reflected against the background of Cultural Theory	149
9.2.5	References	158
9.3	Appendix of the assessment of legal aspects in HTA: Common legal provisions within the EU	159
9.3.1	Provisions concerning the patient	159
9.3.2	Specifications concerning the technology	160
9.3.3	References	165

List of Tables

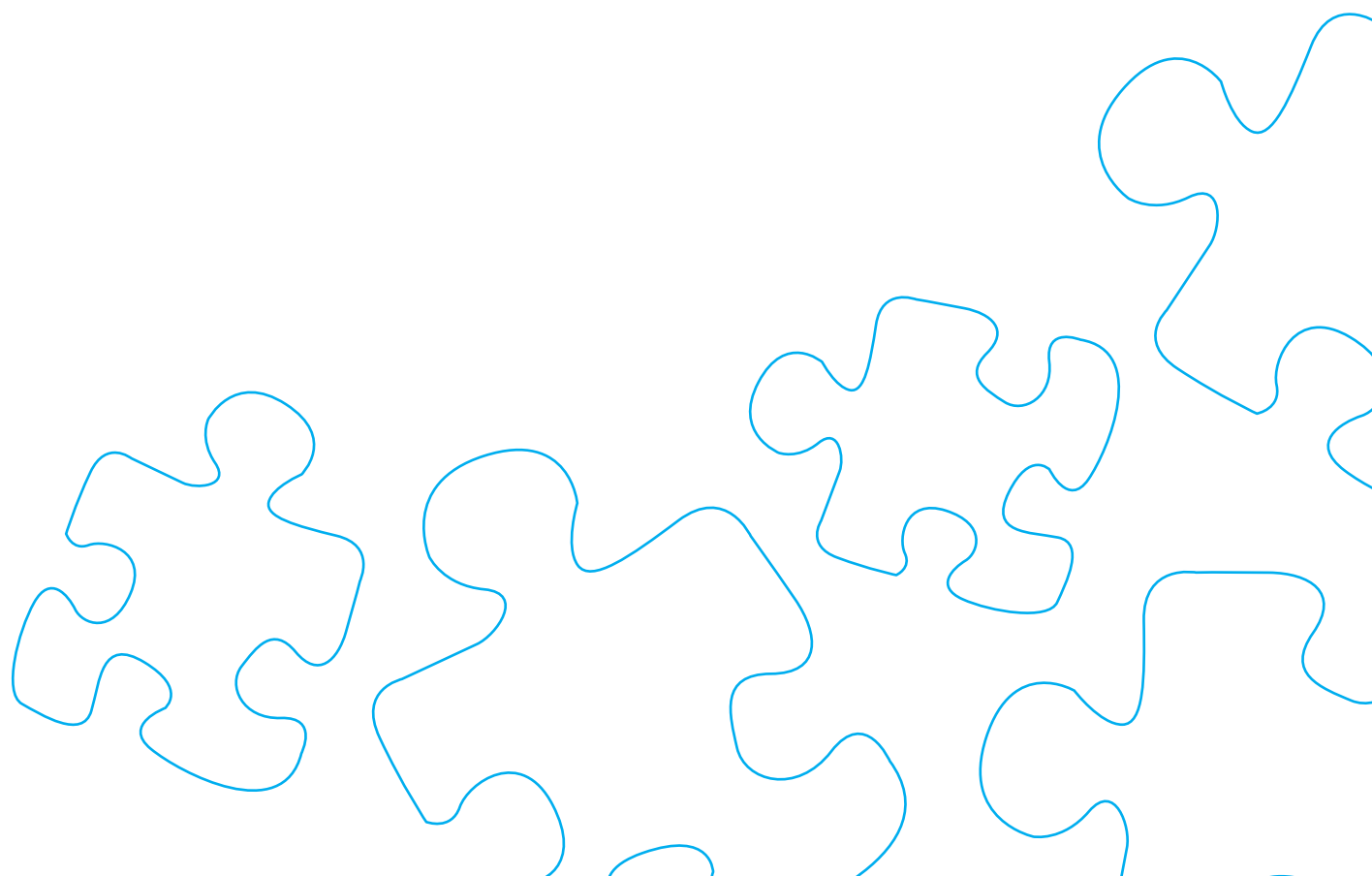
Table 1:	Synthesis of potentially relevant characteristics of complexity in HTA.....	18
Table 2:	Aspects of complexity potentially related to the technology or the system, and the implications for an effectiveness assessment, as well as examples from the case study on reinforced home-based palliative care	25
Table 3:	List of studies from the two journal special issues that informed the guidance for effectiveness assessment. The gray boxes denote those studies that were of particular relevance	26
Table 4:	Meta-analytical and other quantitative methods for evidence synthesis, as well as their relevance to complex interventions outlined by Petticrew et al. 2013	32
Table 5:	Stakeholders as customers, actors and owners	49
Table 6:	Stakeholders in the reinforced palliative home care case study	50
Table 7:	Aspects of complexity in the reinforced palliative home care case study.....	53
Table 8:	Synthesis of most relevant characteristics of complexity for addressing moral issues in HTA.....	62
Table 9:	Some implications of synthesised relevant complexity characteristics for ethical analyses in HTA	63
Table 10:	Meanings of the term integration relevant for ethical analyses in HTA.....	63
Table 11:	Presentation of selected ethical approaches.....	64
Table 12:	Summary of ethical approaches to HTA according to aspects of complexity.....	70
Table 13:	Assessment of merits of various ethics approaches according to various meanings of integration.....	72
Table 14:	Applicability of ethics approaches according to assessment versus appraisal aims	73
Table 15:	Features of ethical approaches in HTA to consider for amending or supplementing purposes in cases of complex technologies	74
Table 16:	Framework main category: Social construction/ understanding of health issue.....	85
Table 17:	Framework main category: Social image of technology and use	86
Table 18:	Framework subcategory: Perceived usefulness and the idea of benefit	87
Table 19:	Framework subcategory: Knowledge about and understanding of technology.....	88
Table 20:	Framework subcategory: Attitudes and acceptance of technology and use	89
Table 21:	Framework subcategory: Risk perception and handling.....	90
Table 22:	Framework main category: Socio-cultural aspects of implementation of technology /organization of technology use	91
Table 23:	Framework subcategory: Socio-cultural aspects of target group	92
Table 24:	Framework subcategory: Social inequality and technology use	93
Table 25:	Framework subcategory: User-professional-relationships and decision making	94
Table 26:	Framework subcategory: Relationships between professionals providing the technology	95
Table 27:	Framework main category: Social construction/understanding of health issue.....	149

Table 28: Framework subcategory: Perceived usefulness and the idea of benefit	150
Table 29: Framework subcategory: Knowledge about and understanding of technology.....	151
Table 30: Framework subcategory: Attitudes and acceptance of technology and use	152
Table 31: Framework subcategory: Risk perception and handling.....	153
Table 32: Framework subcategory: Socio-cultural characteristic of target group.....	154
Table 33: Framework subcategory: Social inequality and technology use	155
Table 34: Framework subcategory: User-professional-relationships and decision making	156
Table 35: Framework subcategory: Relationships between professionals providing the technology	157

List of Figures

Figure 1: INTEGRATE-HTA process model for integrated assessment of complex technologies.....	17
Figure 2: Steps to facilitate a decision on the appropriate methods for study design inclusion and evidence synthesis	27
Figure 3: Harvest plot showing technology effects for lay caregiver outcomes, in review of reinforced home-based palliative care.....	35
Figure 4: Harvest plot assessing whether effects for lay caregiver outcomes are better for COPE interventions compared to other interventions.	39
Figure 5: The HTA economic modelling system	47
Figure 6: Problem structuring activities	48
Figure 7: Health and wellbeing logic model for reinforced palliative home care.....	55
Figure 8: Framework for ethical analyses in HTA of complex technologies	66
Figure 9: Process for selecting ethical approach	67
Figure 10: Overview of the socio-cultural aspects represented in the socio-cultural framework	84
Figure 11: Assessment process for the assessment of socio-cultural aspects	96
Figure 12: Localisation of Legal Aspects in HTA	104
Figure 13: Overview of conceptual modelling framework for economic modelling of complex interventions.....	132
Figure 14: The two dimensions of sociality and the four rationalities	145

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



1 INTRODUCTION

1.1 PURPOSE AND SCOPE OF THE GUIDANCE

The purpose of this guidance is to provide concepts, frameworks, approaches and methods that facilitate health technology assessment (HTA) of complex technologies¹. It comprises five aspects of assessment: effectiveness, economic, ethical, socio-cultural and legal aspects. Other aspects, such as safety and organizational aspects are not addressed explicitly, but some are implicitly addressed by one or more of the other aspects.

1.1.1 Aim of this guidance

Complex health technologies have become increasingly important in response to the changing disease patterns in the European population, as well as progress in medicine and health care. Complex technologies challenge traditional methods in HTA and make the assessment of ethical, socio-cultural and legal aspects especially relevant, i.e. aspects that still easily get ignored in HTA.

This guidance comprises five aspects of HTA: effectiveness, economic, socio-cultural, ethical and legal. Altogether, the guidance is aimed at a comprehensive assessment that is sensitive to the challenges of complex health care technologies. It provides guidance on how to choose between different methods, approaches, frameworks and procedures, how to use them, and how to modify them if necessary, depending on the goal of the assessment and the (type of) complexity of the technology.

1.1.2 Target audience for this guidance

The target audience of this guidance is HTA researchers engaged in any aspect of HTA, stakeholders using and planning to do HTAs, as well as the interested public. Application of the guidance should be possible for those without specific education and extensive training in each of the HTA assessment aspects, i.e. beyond the qualifications that HTA researchers normally have. However, because of the more demanding tasks required by HTAs of complex technologies, some specific expertise may be required in part of the assessment process. The guidance will increase the users understanding of the assessment of complex technologies and the methodological challenges and solutions involved.

1.1.3 The added value of this guidance in relation to existing guidance

This guidance relates to existing sources that provide a methodology to assess health technologies, such as the HTA Core Model (EUnetHTA, 2015), and the Health Technology Assessment Handbook (Kristensen & Sigmund, 2007). These and other sources are available through the portal of Health Technology Assessment international (HTAi).² For assessing effectiveness, economic and ethical aspects of HTA there are a wealth of existing resources, methodological guidances and approaches. For these aspects the INTEGRATE-HTA guidance does not seek to replace these, but rather to complement and expand on existing methods of particular relevance when considering complex technologies. For the assessment of socio-cultural and legal aspects there are less methodology guidances available. Hence, these parts of the INTEGRATE-HTA guidance provides new developed methods in addition to existing methods.

The guidance for **effectiveness** assessment focuses on choosing the type or types of evidence to be included in the review from a heterogeneous range of options, and choosing a method for evidence synthesis from a spectrum of available methods. The guidance aims to help those conducting effectiveness assessments gain a comprehensive understanding of the scope of the review, the technology, the complexity that may influence these aspects, and the methods available, and based on these aspects to make an appropriate decision about the methods to be used.

The guidance on **economic** aspects in HTA, examines how current guidelines for economic evaluation address characteristics of complexity. The economics guidance provides practical advice on the application of a systems approach to economic evaluation of complex interventions in complex settings and highlights areas where further methodological research is required in order to adequately respond to the issues raised by complexity.

The **ethical** guidance explicitly refers to the most used and referred methods in the field (e.g. Principlism, Social Shaping of Technology, the Socratic approach etc.) and offers guidance for selecting among existing methods, in order to fit the requirements of complex health technologies when delivered in the local context. In addition, it offers guidance on how to modify existing and/or expand methods in order to meet these requirements.

For **socio-cultural** aspects the guidance facilitates the identification and evaluation of social and cultural aspects from different perspectives as well as at different levels of social organisation. It offers an inductively developed socio-cultural framework and a stepwise assessment process. Methodological and theoretical approaches are pre-

¹ The concept of complex technology is explained in chapter 1.2.1.

² <http://vortal.htai.org/?q=selected-resources>

sented with their implications, strengths and limitations. The reflection of the socio-cultural framework against the background of Cultural Theory offers a way to identify and address cultural heterogeneity of different social groups.

The guidance on **legal** aspects focus on nine legal core issues, which have been identified as being most relevant for HTA. Although these aspects have been addressed in the three existing approaches, these approaches mostly require a legal education to be applicable. The guidance provide support to non-legally trained HTA-doers to identify legal issues, which require further inquiry within the respective HTA. By pointing out connections of legal aspects to other aspects as well as to the respective relevant level of decision-making the guidance allows for forgoing deeper assessments of legal issues of minor importance for the specific HTA and with that make the assessment of legal aspects faster and easier to conduct.

1.1.4 How this guidance relates to an integrated assessment process

In order to achieve an integrated HTA, the application of the methodological guidances is structured into a systematic assessment process to strive for integration from the very beginning of the HTA. The INTEGRATE-HTA Model consists of five steps (Wahlster et al., 2016). After an initial definition of the HTA objective and the technology in accordance with the support of the stakeholders in step 1, the specific logic model in step 2 provides a structured overview of the factors and aspects surrounding the technology. Patient characteristics, context and implementation issues inform the assessment of effectiveness, and economic, ethical, legal, and socio-cultural aspects in step 3. In Step 4, a graphical overview of the assessment results structured according to the HTA objective and the logic model is created. Finally, the presentation of the results in step 5 forms the basis for a structured decision-making process.

This joint guidance provides methods for the assessment of five aspects of HTA (effectiveness, economic, ethical, socio-cultural, and legal aspects). These methods can be applied in a stand-alone manner, but applying them as part of the INTEGRATE-HTA Model provides a much more comprehensive, iterative, and integrated process. As indicated by the highlighted fields in Figure 1, the methods and results for the individual assessment aspects inform the INTEGRATE-HTA Model at multiple stages. Early in the HTA process in step 1 the various scoping exercises undertaken as part of the individual assessment aspects feed into the overall HTA scope. At a later stage, in Step 3, effectiveness, economic, ethical, socio-cultural and legal assessments are conducted, and this information subsequently informs the creation of the Extended Logic Model to Map the Assessment Results (ELMMAR Model). This model summarizes and presents the results of the various assessments and the interrelationships, and is used to directly inform the HTA decision.

1.2 BACKGROUND

We understand and use the term *health technology* in a broad sense and embracing among other *health care interventions*, which is in accordance with the INAHTA (2015) definition of *health technology*: “An intervention that may be used to promote health, to prevent, diagnose or treat acute or chronic disease, or for rehabilitation. This includes the pharmaceuticals, devices, procedures and organizational systems used in health care”.

Despite considerable achievements in recent years, contemporary HTA is only partially equipped to assess complex technologies.

1.2.1 Complexity

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 (MRC 2008). 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.

Figure 1: INTEGRATE-HTA Model for an integrated assessment of complex technologies.

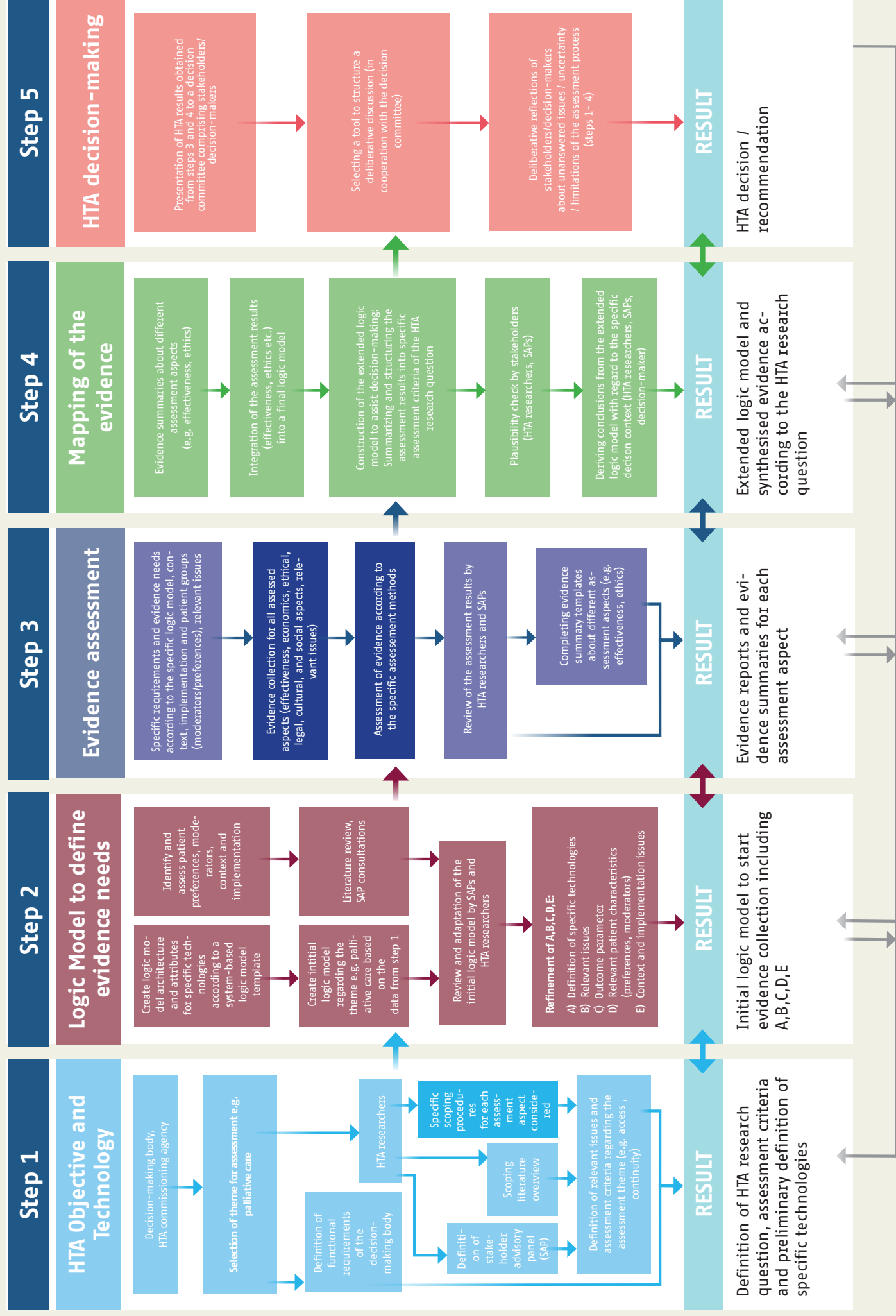


Table 1: Synthesis of potentially relevant characteristics of complexity in HTA.

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 dependency	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.

Consequently, When starting an assessment *on (any) health technology* these factors should be carefully reviewed with the purpose to

1. describe the complexity of an intervention and the system within which it acts,
2. understand whether this complexity matters for decision making and therefore needs to be addressed in an HTA,
3. understand the implications of complexity for the methods of HTA analysis in assessing the ethical, legal, effectiveness, economic and socio-cultural aspects of an intervention,
4. expose important factors that decision makers need to consider in interpreting the HTA.

1.3 GUIDANCE DEVELOPMENT

The point of departure differs between the five aspects addressed in the joint guidance here: effectiveness and economic analyses have well established methods, while the development of specific methods for socio-cultural and legal assessment in HTA is in an early stage. Ethical analyses in HTA are in an intermediate

position where a lot of methods have been introduced, but the documentation of their application is sparse. Hence, the development of each part of this guidance had different point of departures and followed different tracks. This is outlined in the respective chapters.

1.4 APPLICATION OF THE GUIDANCE

This guidance consists of five parts (effectiveness, economy, ethics, socio-cultural and legal aspects) which could be used separately to analyse a single aspect, as well as for an integrated assessment, e.g. to inform a scoping exercise at the beginning of the HTA procedure, see Wahlster et al. (2016). The integration by addressing the different aspects in a comprehensive HTA is strongly recommended.

1.4.1 Interrelationships between the five aspects of the guidance

From the definition of HTA given by the World Health Organization (2015) it should be clear that HTA should ideally be a comprehensive method of assessment: "...the systematic evaluation of proper-

ties, effects, and/or impacts of health technology. It is a multidisciplinary process to evaluate the social, economic, organizational and ethical issues of a health intervention or health technology. The main purpose of conducting an assessment is to inform a policy decision making." However, in reality economic and effectiveness assessments seem to receive most attention. Other aspects are less considered, although ethical, socio-cultural, and legal aspects are critical to understand the impact of a health intervention and the way it interacts with the socio-cultural environment. For complex technologies with high social impact, these aspects may be the most important.

The philosophy of a truly integrated HTA that underpins INTEGRATE-HTA emphasizes the importance, not only of considering multiple assessment aspects, including effectiveness, economic, socio-cultural, ethical and legal aspects individually, but of considering how these aspects are related, and how these interrelationships affect the assessment process and outcome.

Assessing each aspect in a stand-alone matter may prove insufficient within HTA. Interrelationships between all of the five assessment dimensions exist, and may have implications for the intervention impact or for the assessment of impact. For example the idea of benefit is clearly culturally shaped – as the example of Cochlear Implants (CI) shows. CI³ is a well-known example of a technology for which the interrelationships of various assessment aspects proves important within the HTA. For CI, an assessment of effectiveness or efficiency, including the choice of appropriate outcomes, is not straightforward, as deafness is a topic that touches on many socio-cultural and ethical aspects (Hyde & Power, 2006). Deafness can be viewed as a medical disability or as a characteristic of a specific socio-cultural group (using sign language), and to what extent each of these perspectives is considered may have impacts for all assessment aspects.

Integrated assessment of complex health technologies (Wahlster et al., 2016) of the INTEGRATE-HTA project provides guidance on systematic integration across all assessment aspects, and emphasize that the integration is a process that needs to start at the beginning of the HTA and the importance of involving stakeholders in all steps of the process.

Collaboration and exchange is necessary as there are overlaps which need consideration if assessment aspects are being dealt with by different persons or wor-

king groups. The question of overlaps is particularly relevant for ethical and socio-cultural aspects, which also can be addressed together (e.g. in a common literature search) (Lehoux & Williams-Jones, 2007). Furthermore, ethical and socio-cultural norms form the regulation of health technologies in terms of legal norms. Moreover, the interrelation between ethical and socio-cultural norms and legal norms also becomes apparent in the interpretation of legal norms, which is often based on social or ethical consideration of legislators, administrators, or judges. Legal norms in turn can influence ethical and social values for example by ordering or sanctioning ethically or socially in-/adequate behaviours. There are also inherent links between the economics and the effectiveness assessment aspect, which means that a close sharing of identified primary evidence, of extracted results, and of synthesized evidence is beneficial in assessing both assessment aspects.

³ A cochlear implant is a medical device aimed to restore hearing of patients with moderate or severe sensorineural hearing loss. The device consists of a speech processor that transfers sounds to the acoustic nerve through electrodes and an external microphone. The cochlear implant will be placed through surgery and the patient needs extensive rehabilitation for optimal use of the device (Reuzel, van der Wilt, ten Have, & de Vries Robbe, 2001).

2 GUIDANCE TO ASSESS EFFECTIVENESS ASPECTS

By: Jacob Burns, James B. Chilcott, Ralph van Hoorn, Wietske Kievit, Eva Rehfuss

2.1 INTRODUCTION

2.1.1 Purpose and scope of the guidance

Aim of this guidance

The aim of this guidance is to give an overview of existing methods for assessing the effectiveness of complex technologies, and to describe under what circumstances these methods may be appropriate. For the purpose of this guidance, effectiveness will refer to the extent to which a technology improves desirable outcomes. These outcomes may be health-related, but may also be non-health-related, encompassing, for example certain process, intermediate or surrogate outcomes. Efficacy, which often differs from effectiveness in that it usually refers to the effect under ideal rather than real world circumstances, and safety are however not considered as part of effectiveness in this guidance.

It is meant for those researchers looking to evaluate the effectiveness of complex technologies, based on the existing primary evidence base, either as part of an HTA, or as part of a stand-alone systematic review of effectiveness. Complexity, which is discussed in detail in another section 1.2.1, may have implications for all steps of the assessment, from scoping to the final steps of interpreting results. The interest in evaluating complex interventions and technologies has grown steadily over the last years, and accompanying this trend there has been an increasing realization that traditional systematic review and evidence synthesis methods may not always be well suited to such assessments. This guidance will specifically focus on two aspects of the effectiveness review process, for which complexity has important implications: the inclusion and handling of heterogeneous evidence and the evidence synthesis process. It should:

- Give an overview of existing methods and provide guidance for **dealing with heterogeneous study designs** in effectiveness reviews of complex interventions, and
- Summarize existing methods and provide guidance for **choosing an appropriate method for evidence synthesis** in effectiveness reviews of complex interventions.

How does this guidance relate to other similar guidances in the field?

A source that many reviewers turn to for guidance on producing effectiveness reviews is the Cochrane Handbook for Systematic Reviews of Interventions, published by the Cochrane Collaboration (Higgins & Green, 2011). With over 5000 published reviews to date, the primary aim of the Cochrane Collaboration is to help people make well-informed decisions about health care by preparing, maintaining and promoting the accessibility of systematic reviews (Cochrane Online). The handbook provides guidance on all parts of the review process, from question definition and protocol development through to interpretation of results and drawing conclusions, and review authors are expected to adhere to rigorous methodological quality at all levels. The Cochrane Collaboration promotes a mostly standard set of methods, including tight inclusion criteria with regard to study design and evidence synthesis with meta-analysis (MA) or a narrative summary. Some newer reviews have expanded the criteria for study designs, and supplemental qualitative reviews have also been published recently.

Another major source of guidance for those producing effectiveness reviews of interventions or technologies, specifically within the context of HTA, is the EUnetHTA (the HTA Core Model). The HTA Core Model is a methodological framework for collaborative production and sharing of HTA information, which defines the content elements to be considered in an HTA and enables standardized reporting. The HTA Core Model divides the HTA into nine domains, of which clinical effectiveness is one. It provides a general yet comprehensive guide for those assessing effectiveness in HTA, guided by the questions of efficacy and effectiveness: "Can this technology work and does this technology work in practice?" (Core Model).

A further source of guidance for both HTA and systematic reviews of effectiveness is the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) approach, which focuses on rating the quality of evidence and grading the strength of recommendation for the technology being assessed (Guyatt et al., 2008). Within the GRADE approach, emphasis is placed on formulating an appropriate research question, specifying populations, technologies and comparators of interest, and identifying and prioritizing outcomes. These steps are important because they allow for the summary of all relevant evidence, and for the rating of the quality of evidence and grading the strength of a recommendation. GRADE aims to make such judgements explicit and transparent, and helps researchers and decision makers

to move from the evidence to a decision (Guyatt et al., 2011).

With regard to completing an assessment of technology effectiveness from start to finish, both the Cochrane Handbook for Systematic Reviews of Interventions and the HTA Core Model are comprehensive in nature. This guidance does not aim for this level of comprehensiveness, nor is it meant to replace either of these. This guidance specifically focuses on two particular aspects of the process, the handling of heterogeneous study designs and choosing an appropriate method for evidence synthesis. It is meant, therefore, to complement existing resources, especially with respect to assessing the effectiveness of complex technologies, where this complexity should be considered, and may substantially shape the assessment.

2.1.2 Background

As described above, this guidance is structured around the inclusion and handling the heterogeneous study designs, which often form the primary evidence base for complex technologies, and the various evidence synthesis methods available for assessing the effectiveness of these technologies.

Existing approaches and limitations

Inclusion and handling of heterogeneous study designs

For effectiveness reviews of complex technologies, a potentially broad research question as well as an intricate, multidisciplinary search often lead to the collection of very heterogeneous evidence, with a potentially wide range of methodological characteristics, included populations, technologies, comparisons, outcomes and results. The identification and subsequent inclusion of heterogeneous study designs has important implications for the systematic review process and outcome (Reeves et al., 2013). The gold standard randomized controlled trial (RCT), the mainstay of the traditional systematic review due to its potential avoidance of bias (Grimes & Schulz 2002), may not be the most feasible or appropriate for certain technologies, and much evidence may rest within other study designs (Higgins et al., 2012). The “inverse evidence law”, for example, postulates that for wider social economic and environmental determinants of health, very little evidence on technology effectiveness exists, and that existing evidence will likely include non-randomized studies (Nutbeam, 2001). The question

“How low do you go?” proposed in Ogilvie et al, refers to the issue of what type of evidence to include in systematic reviews of effectiveness, and has been an area of much thought and research (Ogilvie et al., 2005).

Evidence hierarchies, in which study designs are organized by decreasing quality, have been used in the past to determine study design inclusion. RCTs, for example, often represent the pinnacle of evidence quality for primary research, and are consequently often the only study design included in systematic reviews (Eccles et al., 1996; NHMRC, 1998). This practice is implemented in many reviews published by the Cochrane Collaboration, known for the production of methodologically rigorous, high quality systematic reviews.

Another possible approach, as practiced by the Cochrane Effective Practice and Organisation of Care (EPOC) Group and Cochrane Public Health, among a handful of others, involves including certain nonrandomized study designs, which have been rigorously performed and therefore have minimized risk of bias. Reviews applying the EPOC criteria for study design inclusion accept, in addition to RCTs and cluster RCTs, non-randomized trials, controlled before-after studies (CBA) where at least two intervention and two control sites exist, and interrupted time series (ITS) studies where at least three data points before and three data points after intervention were measured (EPOC 2013).

It is now generally accepted that for many effectiveness reviews, inclusion of nonrandomized studies (NRS) may be necessary, possibly even those with a higher risk of bias than those considered by EPOC as described above. Consequently, many aspects regarding search strategy, screening, data extraction, risk of bias assessment (Higgins et al., 2012) and evidence synthesis (Valentine & Thompson, 2012) must be carefully considered. The question of which NRSs to include arises as a variety of study types exists, sometimes with conflicting labels and definitions, and as the study types included may potentially affect the resulting technology effectiveness (Higgins et al., 2012). Higgins et al, as part of a Research Synthesis Methods Special Issue Paper dealing with inclusion of NRS, support the use of specific study design features, rather than study designs, to decide upon inclusion. This approach allows for inclusion of studies that satisfy important methodological requirements for avoiding bias regardless of design labels, and helps avoid excluding studies due only to conflicting terminology or poor labelling (Higgins et al., 2012). Box 1, below, includes the specific study design features from this series, deemed appropriate for determining study inclusion.

Box 1: Specific study features for determining study inclusion, as published in the Research Synthesis Methods Special Issue Paper dealing with the inclusion of NRS

Was there a relevant comparison:

- Between two or more groups of participants receiving different interventions?
- Within the same group of participants over time?

Were groups of individuals formed by:

- Randomization?
- Quasi-randomization?
- Other action of researchers?
- Time differences?
- Location differences?
- Healthcare decision makers?
- Participants' preferences?
- On the basis of outcome?
- Some other process? (specify)

Were the features of the study described below carried out after the study was designed:

- Identification of participants?
- Assessment before intervention?
- Actions/choices leading to an individual becoming a member of a group?
- Assessment of outcomes?

On which variables was comparability between groups assessed:

- Potential confounders?
- Assessment of outcome variables before intervention?

So far, the above-listed rationale for including specific study designs or studies satisfying particular study features is based on the principle of avoiding or minimizing the introduction of bias from primary studies into the systematic review. For some reviews, however, the question of overall effectiveness, as measured by a precise, pooled estimate of effectiveness, may be less important than others, such as "Does the technology show a positive or negative effect across many different contexts?", "In what populations is the technology most effective?", "What technology component or combination of components are most effective?", "In what contexts is the technology most effective?" (Squires et al., 2013). In such reviews, tightly controlled RCTs assessing a very specific population, technology and set of outcomes may minimize the risk of introducing bias into the review results, but may not address the questions central to the review. In contrast, certain NRSs may prove more informative and appropriate (Reeves et al., 2013, Schünemann, 2013).

Another active field of research relates to the recognized necessity and benefits of including NRSs in certain re-

views, and thus deals with identifying and quantifying potential biases of included NRSs, and subsequently adjusting for these. Such bias adjustments have been applied for including different types of observational studies (Turner et al., 2009; Thompson et al., 2010).

A converse approach to a systematic review with very selective inclusion criteria, only including RCTs or high rigor NRSs, involves inclusion of studies regardless of study design or design features. This is a potentially dangerous practice, if conclusions are not cautiously drawn and limitations made transparent, as it may overstate conclusions from studies that are likely biased.

Several reviews exist, which describe the utilization of NRSs in a specific subsample of the medical literature. Deeks et al. for example, performed a review of eight systematic reviews which synthesized both randomized and nonrandomized studies, showing that in some reviews, the two types of evidence agreed well, while in others strong disagreement was present (Deeks et al., 2003). Rockers et al. and Glenton et al, both working in the field of health systems research, showed that the degree to which NRS are included, as well as which spe-

cific study designs are included, varies widely, and that for some review topics where NRS inclusion was considered, a lack of such published studies exists (Rockers et al., 2012; Glenton et al., 2013)

Thus far, the methods outlined are relevant for effectiveness reviews in which only quantitative data are considered, and in many cases quantitative studies are sufficient in assessing the effectiveness of health technologies or interventions. It is becoming more accepted, however, that both qualitative and mixed-methods reviews can be useful either as a complement to quantitative reviews or as stand-alone products for assessing certain aspects of effectiveness. Insights from qualitative studies can facilitate the exploration of differences and similarities across populations, contexts, technology design, delivery and implementation aspects and methodological characteristics (Khan et al., 2008; Hannes & Lockwood, 2012). It has also been argued that the use of qualitative and mixed-methods research may make systematic reviews more relevant, by enhancing the utility and impact of findings, and increasing the ability of findings to inform policy and practice (Harden, 2010).

A recent guidance published by the Medical Research Council (MRC) in the UK also stresses the importance of process evaluation in the evaluations of a complex technology, as it highlights what technology was delivered, how it was delivered, how much of it was delivered, and by and to whom it was delivered (Moore et al., 2015). When assessing a complex technology in an effectiveness review, such information can be critical in understanding how and why a technology is effective or not.

Although each of the above-listed types of evidence and approaches to handling their inclusion may have advantages in certain situations, it is clear from the wide range of results seen in reviews of NRS utilization that clear guidance is lacking for those performing effectiveness reviews of complex technologies.

Evidence synthesis methods

The most common form of evidence synthesis within systematic reviews is meta-analysis (MA), in which results from multiple studies are pooled and a common technology effect is calculated. This pooled effect, as well as individual study effects can then be neatly portrayed using a forest plot (Higgins & Green, 2011). It is well documented, however, that this standard approach is not always well suited to reviews of complex technologies (Ogilvie et al., 2008; Turley et al., 2013), which are often evaluated by, as described above, a very heterogeneous

body of evidence. In such instances as described above, it may be important not to simply understand overall effectiveness through statistical pooling, but to understand in what populations or sub-populations, and in what settings or contexts the technology was effective (Craig et al., 2008; Petticrew et al., 2013). Assessing heterogeneity among primary studies, which may be methodological (e.g. differences in study design, outcome definition, blinding, etc.) or clinical (e.g. differences in study population and technology-related aspects) may also help explain trends in effectiveness, and may be of interest. Subgroup analyses allow reviewers to investigate such questions, but only as long as statistical pooling is appropriate. The usual alternative to MA, when heterogeneity precludes statistical pooling, tends to be a narrative summary. Such a narrative summary, however, especially where a large and diverse evidence base is identified, often fails to provide a clear indication of findings and may not be very accessible to decision makers wishing to use the results of a systematic review. A wealth of different options exists for synthesizing evidence in systematic reviews of complex technologies, ranging from the simple, concise, graphical portrayal of the harvest plot (Ogilvie et al., 2008) to complex meta-analytical methods like network MA (Jackson et al., 2011), and the most appropriate method may be situation-dependent. A wide range of quantitative methods is available, and qualitative and mixed methods are also available, and can be appropriate and informative, especially when dealing with complex technologies and systems. Petticrew et al. have documented and described several options for synthesizing evidence of complex technologies, spanning from complex meta-analytical methods to mixed-method approaches to qualitative methods (Petticrew et al., 2013).

Impressive work has been done in the documentation and description of alternatives to MA and narrative synthesis, but clear guidance, which helps reviewers decide on an appropriate synthesis method given the specific review question, as well as the specific context, technology and evidence base, is lacking and would be a valuable resource to those performing HTAs or stand-alone effectiveness reviews of complex technologies.

2.1.3 Complexity and integration perspectives

The issue of complexity, and how it was approached overall within WP3 is discussed in detail elsewhere (1.2.1), but some considerations may be specific to the

assessment of effectiveness. Technology complexity, as well as overall system complexity, have major implications for all stages of an effectiveness assessment, from defining the review question to the final stages of results interpretation. Such complexity has wide-reaching implications for deciding what types of evidence to include in the review and for deciding what method of evidence synthesis to apply, decisions which potentially greatly influence the results of the assessment (Noyes et al., 2013). Below in Table 2 are aspects of complexity that may influence the assessment of effectiveness as well as the effectiveness of complex technologies. Also included in the table are examples of the aspects of complexity, as encountered in the INTEGRATE-HTA case study on reinforced home-based palliative care.

In other words, the presence of system and technology complexity potentially means that a broad range of aspects regarding specific subgroups, technology components, delivery, implementation and context may be of interest when assessing effectiveness (Petticrew et al., 2013). It also means that the primary evidence to be synthesized may be very heterogeneous, with regard to both clinical and methodological characteristics, i.e. that the primary literature may have assessed a range of different technologies in a range of different populations and contexts against a range of different outcomes using a range of different study designs and methods (Pigott & Shepperd, 2013). As emphasized in the WP3 section on complexity (1.2.1), the formal mapping of complexity should be the starting point in the assessment of a complex technology, and such an exercise is extremely important in the effectiveness assessment.

2.2 GUIDANCE DEVELOPMENT

Three main sources informed the main guidance developed. These, described in more detail below, include:

- Series of journal articles focusing on methodological developments in systematic reviews of effectiveness,
- Other INTEGRATE-HTA guidances,
- Effectiveness reviews of complex technologies, conducted by members of the guidance team.

In producing a coherent and comprehensive guidance dealing with both the inclusion and handling of heterogeneous evidence and selecting an appropriate method for evidence synthesis we attempted to move beyond these individual sources. To this end, we aimed to define a series of aspects for the reviewer to consider, which, in doing so, would help guide the reviewer to include

appropriate evidence and choose an appropriate method for synthesizing this evidence.

2.2.1 Series of journal articles, focusing on methodological developments in systematic reviews of effectiveness

The development of this guidance was strongly influenced by two recent series of journal articles, which dealt specifically with methodological developments in systematic reviews of effectiveness. These were:

- A Journal of Research Synthesis Methods Special Issue, focusing on the inclusion of NRS in systematic reviews of effects of health interventions (Reeves et al., 2013),
- A Journal of Clinical Epidemiology series of methodological articles on considering complexity in systematic reviews of interventions (Anderson et al., 2013a).

These sources were chosen because they represent the current state of the art for methodology in effectiveness reviews of complex interventions. The two journal series, summarized below in Table 3, help the reader obtain a holistic understanding of complexity and the use of NRS in SRs, and the implications for various stages of the review. Due to the specific focus of this guidance on the handling of heterogeneous evidence and evidence synthesis, certain articles from these series were especially relevant for and directly informed parts of the guidance development. These, shaded in Table 3, included Petticrew et al., 2013, Squires et al., 2013, Pigott & Shepperd, 2013, Schünemann et al., 2013 and Higgins et al., 2013.

2.2.2 Other INTEGRATE-HTA guidances

Work completed as part of INTEGRATE-HTA related specifically to the use of logic models for informing the conduct of systematic reviews and HTAs of complex technologies (Rohwer et al., 2016) strongly influenced the development of the guidance.

2.2.3 Effectiveness reviews of complex technologies

Two systematic reviews undertaken by members of INTEGRATE-HTA, also informed the guidance. These included reviews assessing the effectiveness of interventions to reduce ambient particulate matter air pollution and

Table 2: Aspects of complexity potentially related to the technology or the system, and the implications for an effectiveness assessment, as well as examples from the case study on reinforced home-based palliative care.

Aspect of Complexity	Implications for effectiveness assessment	Example from case study on reinforced home-based palliative care
Multiple and changing perspectives	Including various perspectives into the assessment increases the amount of information to be managed and synthesized. Each perspective, i.e. population group to be assessed, or level of assessment considered, potentially brings further heterogeneity from the primary literature into the analysis.	The delivery and reception of reinforced palliative care involves a wide range of individuals, including many health and social care professionals, the patient, family and lay caregiver(s). These individuals interact with one another in delivering a multi-faceted technology.
Indeterminate phenomena	For complex technologies, it may be difficult to define the technology. This includes drawing a somewhat arbitrary “border” between the technology and the rest of the surrounding system, as well as defining the range of similar technologies to be assessed. A broadly defined technology may lead to a heterogeneous set of included technology.	Relevant reinforced palliative care technologies usually entailed a range of services, and depending on the perspective the reviewer takes, this could include, for example, the specific training for professionals, materials provided to patients and caregivers, services providing physical, psychological, social and spiritual care for patients, as well as respite services and counselling for caregivers. As most primary studies offer a mix of such services, many with some degree of tailoring, studies included in a review may be extremely heterogeneous.
Uncertain causality	Between the technology and outcome, many aspects including interactions between technology components, and aspects of the context and implementation may influence the effectiveness of a technology. If such relevant aspects exist and are of interest, these need to be extracted from the relevant primary literature and included in the analyses. This will add to the amount and heterogeneity of information to be managed and synthesized.	When looking at the system surrounding a reinforced palliative care technology, there are many aspects that could influence the effectiveness, from a range of population characteristics (e.g. diagnosis, time since diagnosis, age) to population-wide political, geographical, socio-cultural context. Additionally, the delivery of the technology is shared by several individuals, and is thus dependent on their behaviours. If such aspects are reported in primary studies, they should be extracted and considered for inclusion in the evidence synthesis.
Unpredictable outcomes	Given the multi-component and multi-faceted nature of complex technologies, it may be necessary to include a range of outcomes to assess their effectiveness. These may change over time, and may be assessed using a variety of differing tools, scales, measures, etc. The consideration of different outcomes and different outcome measures may potentially produce conflicting results.	In a palliative population, including both patients and caregivers, outcomes may change rapidly over time. Additionally, a range of outcomes is important and should be assessed, and many outcomes probably interact with one another (e.g. patient and caregiver QoL). It should be considered whether traditional “hard” outcomes, such as quality of life, depression, etc. are sensitive enough to detect small, yet potentially meaningful changes in a heavily burdened population.
Historicity, time and path dependency	The time, place and context of a technology may influence effectiveness, and these aspects may vary widely among primary studies. For such aspects to be assessed, they must be identified a priori and extracted, which will add to the amount of information to be managed and synthesized.	Palliative care theories and philosophies are ever changing, and this is accompanied by changes in social, political, and health system perspectives. Differences in times, in health systems, in country, etc. may influence effectiveness, and should be considered in an assessment.

Table 3: List of studies from the two journal special issues that informed the guidance for effectiveness assessment. The gray boxes denote those studies that were of particular relevance.

Research Synthesis Methods series focusing on the inclusion of NRS	Journal of Clinical Epidemiology series focusing on considering complexity in SRs
Reeves et al. 2013. "An introduction to methodological issues when including non-randomised studies in systematic reviews on the effects of interventions".	Anderson et al. 2013a. "Introducing a series of methodological articles on considering complexity in systematic reviews of interventions"
Higgins et al. 2012. "Issues relating to study design and risk of bias when including non-randomized studies in systematic reviews on the effects of interventions"	Petticrew et al. 2013.b. "Complex interventions and their implications for systematic reviews: a pragmatic approach"
Valentine & Thompson 2012. "Issues relating to confounding and meta-analysis when including non-randomized studies in systematic reviews on the effects of interventions"	Squires et al. 2013. "Systematic reviews of complex interventions: framing the review question"
Norris et al. 2012. "Issues relating to selective reporting when including non-randomized studies in systematic reviews on the effects of healthcare interventions"	Anderson et al. 2013b. "Investigating complexity in systematic reviews of interventions by using a spectrum of methods"
Schünemann et al. 2013. "Non-randomized studies as a source of complementary, sequential or replacement evidence for randomized controlled trials in systematic reviews on the effects of interventions"	Petticrew et al. 2013.a. "Synthesizing evidence on complex interventions: how meta-analytical, qualitative, and mixed-method approaches can contribute"
Wells et al. 2013. "Checklists of methodological issues for review authors to consider when including non-randomized studies in systematic reviews"	Pigott & Shepperd, 2013. "Identifying, documenting, and examining heterogeneity in systematic reviews of complex interventions"
	Burford et al. 2013. "Assessing the applicability of findings in systematic reviews of complex interventions can enhance the utility of reviews for decision making"
	Noyes et al. 2013. "A research and development agenda for systematic reviews that ask complex questions about complex interventions"

their effects on health (Burns et al., 2014), which is currently underway, and interventions to reduce exposure to lead through consumer products and drinking water, which has been completed (Pfadenhauer et al., 2014). In these two reviews, we applied certain methods for handling heterogeneous evidence and evidence synthe-

sis, in order to assess their usefulness in systematic reviews of complex technologies.

An earlier version of this guidance was applied to the INTEGRATE-HTA case study (Brereton et al., 2016). Based on the experience in applying the guidance, it was revised and re-structured into the present form.

2.3 HOW TO APPLY THE GUIDANCE

As highlighted in 2.1.2, substantial work has been done in describing the range of options and methods available both for the inclusion and handling of heterogeneous study designs and application of evidence synthesis methods. There is no one-size-fits-all solution for the methodology in effectiveness reviews of complex technologies, and for any one review, multiple options may be suitable and appropriate. Nevertheless, based upon certain aspects related to the research question, the technology and the system within which it exists, the resulting complexity, and the available evidence base, certain methods may be more appropriate than others. The aim of this guidance, therefore, is to highlight the aspects that should be considered when making these decisions, and to outline the implications of such considerations in selecting methods. As illustrated in Figure 2, using the following steps to structure the decision process will facilitate deciding upon appropriate methods:

1. Conducting a comprehensive scope of the effectiveness assessment,
2. Gaining a thorough understanding of the characteristics of available methods,

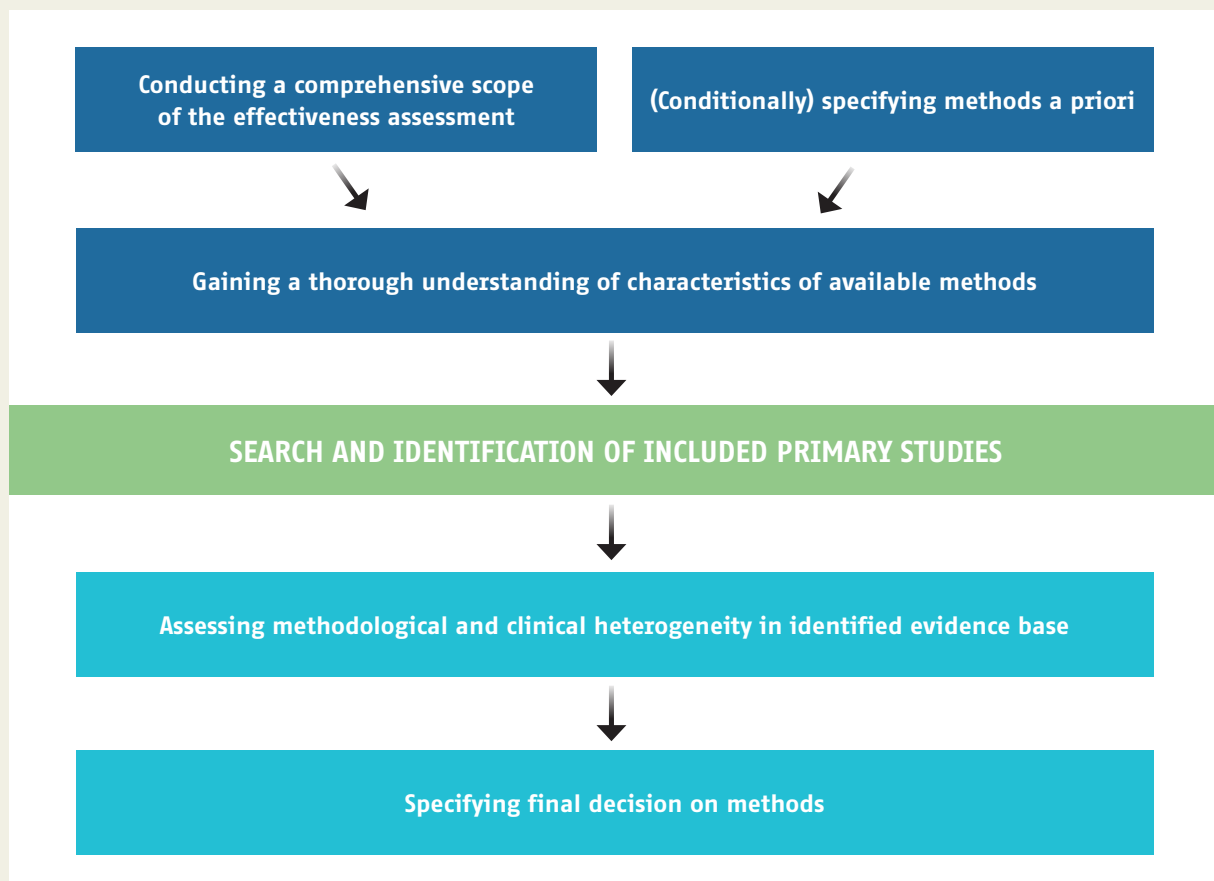
3. (Conditionally) Specifying methods a priori.

For many technologies, these steps, all of which take place at the protocol stage before beginning the review, may be sufficient in deciding upon methods. For other technologies, however, it may still be unclear whether these methods are appropriate, and the decision should thus be treated as conditional. After the searches have been performed, and the potentially relevant studies have been identified, considering these further steps may be necessary:

4. Assessing methodological and clinical heterogeneity in the identified evidence base,
5. Specifying final decision on methods.

These steps are described in detail below. These may not always be sufficient in selecting appropriate methods, and certain steps may be more or less important, depending on the technology, as well as the review and decision context, but thoroughly understanding and considering these steps can help guide the reviewer to an appropriate, review-specific choice.

Figure 2: Steps to facilitate a decision on the appropriate methods for study design inclusion and evidence synthesis.



2.3.1 Conducting a comprehensive scope of the assessment

Research question, PICO and complexity – What question is to be addressed, for whom, when, where?

An early and essential decision in preparing any effectiveness review is to determine its focus (Higgins & Green, 2011; Core Model). This may seem obvious, but for more complex technologies defining the research question, as well as for whom, when, where it should be answered, may be less straight forward. In defining the scope of an effectiveness review, which in turn helps to determine how to set study design inclusion criteria and decide upon a method for evidence synthesis, it is important to consider the effectiveness question of interest, the population, intervention, comparison and outcome (PICO) elements of interest, as well as the complexity inherent to the intervention and system that may have implications for these other aspects.

As described above in 2.1.2, researchers and decision makers may wish to assess one or multiple questions in addition to “Is the technology effective?”, such as “In what populations is the technology most effective?”, “What combination of technology components are most effective?”, “In what contexts is the technology most effective?”, “What are underlying causes of differential effectiveness?” (Squires et al., 2013). Both the Cochrane Collaboration and the HTA Core Model recommend framing the review research question within the PICO scheme, i.e. according to the specific population, intervention, comparison and outcomes of interest (Higgins & Green, 2011; Core Model). For complex technologies, this practice is especially critical in formulating a clear

question that can help to structure the review process, but defining these aspects for a complex technology may be more challenging (Squires et al., 2013). It can likely be assumed that in the planning of an HTA, an overall research question related to the technology of interest and an overall HTA scope will have been defined. The INTEGRATE-HTA Model, for example, as part of (Wahlster et al., 2016) developed an extensive scoping process outlined in Steps 1 and 2. These scoping steps allow for the inclusion of information from the literature, from stakeholder input, as well as from assessments of patient preferences, moderators and predictors of treatment effect (van Hoorn et al., 2016), and context and implementation (Pfadenhauer et al., 2016). This information is collected and structured into a systems-based logic model (Rohwer et al., 2016). This logic model aims to describe the health technology, as well as the system in which it exists, including relevant populations and subpopulations, technology and comparison-related aspects, and outcomes for relevant stakeholders.

As emphasized in Table 2, several aspects of complexity lead to ambiguities with regard to the PICO elements, making it difficult to nail down the focus, especially within the effectiveness assessment, and further development of the research question or questions and PICO scope may be necessary.

Even if a review team does not produce a logic model, when assessing a complex technology, some comprehensive attempt to think about the system within which the technology exists and interactions between different parts of that system, should be made to ensure that the right questions are being asked and documented in a transparent way. This in turn may ensure that the assessment will be helpful and informative for those looking to use it to make decisions.

Box 2: From the INTEGRATE-HTA case study (Brereton et al., 2016)

The initial question regarding effectiveness, formed in the overall HTA scoping, was:

“Are reinforced home care models of palliative care effective in 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?”.

This question, however, is quite general and broad, and for the purposes of the effectiveness assessment further thought and planning went into defining the specific aspects and sub-questions to be assessed – e.g. “For patients with what diagnoses are reinforced models effective?”, “At what point in the patient’s diagnosis should patient and caregiver begin receiving treatment and support?”.

Similarly, the logic model was helpful in forming an initial scope, but further iterations focusing specifically on planning the PICO elements of interest for the effectiveness assessment were needed to define the exact review scope.

State of the primary evidence – What evidence exists for answering the effectiveness question?

The choices of the types of evidence to be included and the methods for evidence synthesis to be applied in an effectiveness assessment largely depend on the nature of the primary evidence base. The review team may have a sufficient overview of the evidence potentially relevant for the review from the initial scoping exercise, but a more targeted inspection, as described below, with regard to both the methodological and clinical state of the evidence, i.e. what study designs have been used to evaluate what types of technologies in what types of participants, outcomes, contexts, etc. may be necessary.

An idea of what study designs have actually been utilized in evaluating the effectiveness of the technology of interest is important in determining what types of study designs should be included. An in-depth scoping of the primary literature, which may include piloting search terms and snowball retrieval and assessment of potentially relevant studies, should allow reviewers to be adequately familiar with the study designs making up the primary evidence base. Furthermore, experts, who are either part of the review team or informing the assessment in an advisory role, may have a good idea of what type of evidence is likely to be identified, and could be consulted. If the reviewers find, for example, that relevant randomized evidence exists, which answers all questions of interest, they may deem further consideration of NRS unnecessary. If, on the other hand, much of the relevant evidence resides in NRS, this would warrant further thought about whether or not, and which types of NRS should be included. This also has implications for the choice of evidence synthesis method, as the question of whether statistical pooling is appropriate or not, depends largely on the range of study designs included.

A scoping of the primary literature with regard to PICO elements of interest, including potentially interesting subgroups, intervention components, context and implementation aspects, as determined in the Research

question, PICO and complexity section should be performed. In the initial scoping, as described above, the goal is to identify all potentially important PICO elements, but this may differ from what has actually been assessed in the primary literature. Scoping the clinical state of the evidence will help the reviewer determine what information regarding particular PICO elements can be found. The reviewer may also evaluate whether the potentially identified studies will likely provide sufficient information for answering the questions of interest, and to what extent clinical heterogeneity will be introduced into the review, and these two considerations will have implications for choosing an appropriate method for evidence synthesis. For example, if the reviewer is most interested in what combination of components leads to the largest effect, yet technologies are rarely described in enough detail to isolate different components, then it might not be possible to address this question. If, on the other hand, a range of components arranged in various combinations has been assessed and reported, an assessment of which combination leads to the largest effect may be possible. At the same time, however, such an evidence base would likely also lead to the introduction of considerable clinical heterogeneity to be managed in the evidence synthesis.

2.3.2 Gaining a thorough understanding of the characteristics of available methods

Methods for handling heterogeneous study designs – “What characteristics of available practices facilitate the assessment of a complex technology?”

As described in 2.1.2, the Special Issue Paper in Research Synthesis Methods dealing with inclusion of NRS supports that for many reviews the inclusion of NRS may be appropriate, but also emphasizes that

Box 3: From the INTEGRATE-HTA case study (Brereton et al., 2016)

This original systematic review (Gomes, 2013), which was updated for in this case study, included RCTs, and NRS of high methodological quality, including CCTs, CBAs and ITS.

Given the number of studies they found addressing the relevant effectiveness questions, and a scoping exercise of the newly published literature, we felt confident that most of the relevant evidence, i.e. the relevant range of services, diagnoses, settings, etc., as included in the systems-based logic model, was captured in such study designs.

the decision to include NRS or not is complex and critical to the usefulness of the review (Reeves et al., 2013). O'Neil et al. identified several reviews including NRS. Reasons given by the various studies for the inclusion of NRS were that insufficient RCT evidence was lacking because they simply had not been conducted, or because conduct of an RCT would be infeasible or unethical, and that existing RCTs lacked generalizability or were of poor quality (O'Neil et al., 2014). A range of NRS exists, including cohort studies, case-control studies, controlled before-after studies, interrupted time-series studies and controlled trials, among others. In addition, a range of other types of evidence has been used in systematic reviews of effectiveness, including process evaluations, modelling studies and qualitative studies. The first decision related to the inclusion of various study designs in most reviews will likely be whether only randomized evidence will be included, or whether various NRS will also be included. If a reviewer decides to include certain NRS, the next decision will be which types. Depending on the review question, the specific technology and the existing evidence base, a further decision might then be, whether there are other types of evidence, e.g. process evaluations, modelling studies or qualitative studies that could provide valuable evidence for the review, and should therefore be included. In determining what types of evidence to include in an effectiveness assessment it is important to consider 1.) the directness of the evidence, defined as "the extent to which the people, interventions, and outcome measures are similar to those of interest," (GRADE Working Group, 2004) and 2.) the potential risk of bias due to including the particular type of evidence. This is certainly situation-dependent, as there is no rule of thumb for what types of evidence will contain what information, and as even studies performed using the same study design can vary widely in risk of bias.

Balancing the use of best available, direct evidence with risk of bias

In the case where no RCTs exist, yet NRS inclusion is not considered, an empty review will be produced. This is not a negative outcome, as it highlights a research gap and can provide a valid justification for further research on a needed topic (Yaffe et al., 2012). In situations where decision makers will imminently make a decision regarding implementation, however, an empty review will provide little useful information, and the use of the "best available evidence" is often

called for. If NRS are included carelessly and indiscriminately without proper consideration and communication of potential biases, biased effect estimates may be produced and subsequently inform decisions (Reeves et al., 2013). Thus NRS should be sought that provide direct evidence for answering the review question and that do not introduce disproportionate bias into the review (Schünemann, 2013).

Directness of evidence

A primary study including a very direct comparison would feature the same, or at least very similar, population, technology, comparison, and outcomes that are of interest for the effectiveness assessment (GRADE Working Group, 2004). A very direct body of evidence would, therefore, include multiple studies, each with a PICO definition very similar to that of the effectiveness review.

In certain situations, depending on the research question and the scope of the review, some study designs may prove to be more direct than others. The RCT, for example, often applies narrow inclusion criteria for participants, implements a specific, controlled variation of the technology, and may assess rather short-term or surrogate outcomes (Schünemann, 2013). For some reviews, such narrow inclusion criteria will not be a problem, and RCTs will provide a sufficiently direct evidence base for informing a decision. Conversely, if the scope of the review is rather broad, i.e. there are various population groups of interest and a technology consisting of many possible components, opportunities for tailoring, etc., or if long-term outcomes or rare events are of interest, then a very narrowly focused RCT will only assess a fraction of the PICO of interest. If several RCTs are identified, each with a very narrow focus, then certain aspects of the broad review scope may not be addressed by the identified randomized evidence. NRS focus may be broader with respect to PICO aspects, or may have assessed the influence of a range of context or implementation-related factors, and thus may provide more direct information for informing reviews of certain complex technologies (Schünemann, 2013).

And it is not only experimental designs like RCTs and NRS that can provide direct evidence relevant for assessments of complex technologies. Where it is important to understand how various technologies were actually carried out, i.e. how the technology was delivered, how much of it was delivered, how it was altered, etc., process evaluations from the relevant

studies can provide rich information for informing the effectiveness assessment (Moore et al., 2015). Similarly, qualitative studies can highlight differences and similarities across populations, contexts, technology design, delivery and implementation aspects, and methodological characteristics (Khan et al., 2008). If such questions are relevant to the effectiveness assessment, then the inclusion of certain process evaluations or qualitative studies may be considered.

Risk of bias

As a result of the randomization process, we expect that prognostic factors are equally distributed between groups, and that they thus differ only with regard to the exposure of interest. Groups within NRS, however, may differ on such prognostic factors, thus effects seen may be attributed to the technology of interest, but they also may be due to prognostic factors (Shrier, 2011). This is a concern, as the synthesis of biased evidence in an effectiveness review only compounds the bias, and will produce a result that is interpreted as credible (Higgins & Green, 2011). It is not so dichotomously simple, however, as RCTs may nonetheless contain selection or other biases, and some NRS may be conducted in such a way that bias is minimized. Many tools exist for assessing the risk of bias, yet most depend on evaluating specific criteria dependent on the specific study design, and tools for evaluating a wide range of evidence are not common (Voss & Rehfuss, 2013). Any effectiveness assessment, regardless of what types of evidence are included or what tools are used to assess the risk of bias, should be clear and transparent in the assessment of risk of bias, and this should be communicated in the review to potential readers and decision makers.

Methods for selecting a method of evidence synthesis – “What characteristics of available methods facilitate the assessment of a complex technology?”

Meta-analytical approaches to evidence synthesis

The traditional method for synthesizing evidence in systematic reviews, the MA, allows the reviewer to address questions about 1.) whether an overall effect exists across a larger body of evidence than an individual study; 2.) whether effects are consistent across studies; 3.) what is the actual magnitude and variation of effects across studies; and 4.) whether particular study-level factors are associated with the magnitude of effect (Petticrew et al., 2013). Variations

and extensions of MA, including subgroup analysis, meta-regression, multi-variate MA, individual participant data MA, hierarchical models and Bayesian MA, allow the reviewer to assess a variety of methodological and clinical issues. These are shown, as outlined by Petticrew et al., in Table 4.

Both the Cochrane Handbook and the HTA Core Model stress the importance of assessing the heterogeneity of included studies, including methodological heterogeneity (e.g. differences in study design, outcome definition, blinding, etc.) and the clinical heterogeneity (e.g. differences in study population and technology-related aspects). Similarly the importance of the assessment of relevant context and implementation factors has been stressed (Wells et al., 2012; Burford et al., 2013), and is covered in another INTEGRATE-HTA guidance (Pfadenhauer et al., 2016). Pigott & Shepperd discussed the importance of considering heterogeneity in systematic reviews of complex technologies, and suggest that heterogeneity is not only something to explain away, but rather something that must necessarily be analyzed and understood in order to ascertain the true effectiveness of a technology (Pigott & Shepperd, 2013). This understanding of how primary studies vary with regard to diverse factors may also help reviewers, decision makers and consumers gain a general understanding of why a technology works in various settings, which would be extremely useful to those deciding whether to implement the technology in a specific setting and context. Several of the methods highlighted in allow for the assessment of different aspects of heterogeneity. Network MA, for example, which allows for the comparison of multiple technologies or combinations of components, even if they were not compared head to head in the primary literature, helps the reviewer and decision makers understand how the makeup of the technology influences the effectiveness or how different components interact. In meta-regression, the reviewer can decide which aspect of clinical or methodological heterogeneity may influence effectiveness and should thus be assessed, making it a very flexible method for assessing the influence of population differences, context differences, or any other factors of interest which differ among included primary studies. Each of the methods highlighted in Table 4 has its own advantages and challenges when applied in reviews of complex technologies, and for in-depth descriptions and examples, the references listed in the table can be consulted. It should be noted that it is important that such analyses of heterogeneity be pre-specified,

Table 4: Meta-analytical and other quantitative methods for evidence synthesis, as well as their relevance to complex interventions outlined by Petticrew et al. 2013.

General description	Relevance to complex interventions
<p>Subgroup analysis: splits the studies or the participants according to population, intervention, or contextual characteristics and examines differences in effect estimates across these subgroups. Characteristics are chosen as those likely to have an impact on the size or direction of the intervention effect. (Borenstein et al., 2009)</p>	<p>Multiple and changing perspectives; uncertain causality</p> <p>Compare subgroups of participants exposed to different intervention components.</p> <p>The impact of major contextual influences (e.g. different implementation mechanisms) can be explored.</p>
<p>Meta-regression: explores the relationship across studies between study characteristics and effect sizes, offering a generalization of subgroup analyses. It draws on the same principles as regression analysis in primary studies, allowing for the effects of continuous and/or categorical variables to be modelled but is conducted at the level of studies rather than at the level of study participants. In addition to testing for statistical significance, the amount of between-study variation in effect sizes that can be explained by the characteristic(s) can be quantified using an index analogous to the R² index in regression analysis of primary data. (Borenstein et al., 2009; Thompson & Higgins, 2002)</p>	<p>Multiple and changing perspectives; uncertain causality; historicity, time and path dependency</p> <p>Explore sources of heterogeneity in effect sizes and their relative importance, for example, in relation to intervention components, degree of tailoring, and various contextual influences</p> <p>Examine phase changes by modelling impact on study duration.</p>
<p>Multi-variate meta-analysis: allows each study to contribute two or more (possibly correlated) effect estimates to the meta-analysis. For example, these may be effects on two outcomes, effects at two time points, or effect sizes for different interventions in the same study. (Jackson et al., 2011)</p>	<p>Unpredictable outcomes; historicity, time and path dependency</p> <p>Can facilitate a joint analysis of intermediate outcomes with downstream outcomes for the same participants, which allows for the correlation in the treatment effects to be estimated.</p> <p>Multivariate meta-analysis of two or more different time points may be used to explore phase transitions</p>
<p>Network meta-analysis: compares multiple interventions simultaneously by analyzing studies making different comparisons in the same analysis. It is a complex form of meta-regression, and if some studies have multiple intervention groups, then it is a multivariate meta-regression. Different components of a complex intervention may be treated as different interventions, and assumptions made about whether the components are additive or interact with one another. (Welton et al., 2009)</p>	<p>Multiple and changing perspectives; uncertain causality</p> <p>Investigation of whether interventions with a particular component (or combination of components) are more effective</p>
<p>Individual participant data meta-analysis: draws on the original research data for each study participant in each included study. Individual participant data meta-analysis is usually conducted in two stages. In the first stage, data in individual studies are reanalyzed in a consistent way. In the second stage, the results of each individual study are combined in a summary estimate of effect, analogous to standard meta-analysis. Alternatively, one-stage methods are available and are an application of hierarchical models. (Higgins & Green, 2011)</p>	<p>Uncertain causality; unpredictable outcomes; historicity, time and path dependency</p> <p>Could overcome problem of many sources of heterogeneity in studies of complex interventions, allowing the analysis to focus on actual differences in intervention type and delivery and potential interactions between interventions and participant characteristics.</p> <p>Very useful for examining outcomes at multiple levels, for example, by conducting analyses for aggregated outcomes.</p> <p>Where outcomes in primary studies were assessed at multiple points in time would facilitate examination of phase transitions</p>

General description

Hierarchical models: are based on the fact that participants are nested within studies that, in turn, are nested within the meta-analysis. Most standard meta-analysis models are hierarchical models, but the idea can be extended to the specific nature of the studies at hand, to account for clustering at various levels. Variability is apportioned to different levels of the hierarchy, for example, in a meta-analysis of cluster-randomized trials, we might have a between-participant component, a (within-study) between-cluster component, and a between-study component. Characteristics of each type of unit can also be modelled using regression approaches. (Raudenbush & Bryk, 2002)

Bayesian methods: follow a different philosophy of statistics from the classic frequentist statistics. Insights gained from new data (i.e. the studies included in a systematic review) are combined with prior knowledge, following the idea of updating knowledge with evidence. In practical terms, prior knowledge is incorporated in meta-analysis by specifying a prior distribution to describe uncertainty in the effect size and/or the likely extent of between-study variation. (Sutton & Abrams, 2001)

Narrative summary methods: may be textual, table-based or graphic-based, and can be used in conjunction with meta-analytical and other quantitative approaches or on their own. The systematic organization and presentation of the data can help the reviewer and reader identify themes across studies and can facilitate the testing of pre-specified theory by exploring similarities and differences among studies.

in order to avoid spurious associations that could potentially mislead review consumers. If ad-hoc analyses are performed, this should be explicitly stated and emphasized in the interpretation of results (Petticrew et al., 2013).

Non-statistical approaches to evidence synthesis

The use of various meta-analytical techniques, in which an overall technology effect is calculated, depends largely on the presence of relatively homogeneous data for comparison. If, however, substantial clinical or methodological heterogeneity is present, then pooling primary studies may be inappropriate

Relevance to complex interventions

Multiple and changing perspectives; uncertain causality; unpredictable outcomes; historicity, time and path dependency

Examine interrelationships between outcomes occurring at different levels

Understand variation in effect due to differences between participants as opposed to variation in effect due to differences between broader aspects of setting.

Bayesian methods: follow a different philosophy of statistics from the classic frequentist statistics. Insights gained from new data (i.e. the studies included in a systematic review) are combined with prior knowledge, following the idea of updating knowledge with evidence. In practical terms, prior knowledge is incorporated in meta-analysis by specifying a prior distribution to describe uncertainty in the effect size and/or the likely extent of between-study variation. (Sutton & Abrams, 2001) Incorporate external evidence (e.g. information on influence of contextual factors) obtained through non-randomized studies or qualitative information.

Uncertain causality; unpredictable outcomes; historicity, time and path dependency

Allows for the examination of trends in effectiveness across various populations, intervention components, contextual aspects, etc.

Allows for the utilization of very heterogeneous evidence (e.g. combination of randomized and non-randomized evidence).

Presenting evidence for multiple outcomes or time points possible.

(Higgins & Green, 2011). One option, if studies are deemed too different to statistically pool, is to produce a forest plot of included studies, yet not calculate a summary effect. Studies can additionally be arranged based on specific aspects, for example all studies assessing a similar subgroup, or applying the same study design can be grouped together. The Cochrane Non-Randomised Studies Methods Group (NRSMG) recommends this practice (Higgins & Green, 2011). Bayesian MA potentially allows for the inclusion of evidence from a range of sources, including data from NRS or qualitative data, and could also help address the issue of extensive methodological heterogeneity.

Alternatively, reviewers could meta-analyze NRS, even in combination with RCTs, after potential biases in the NRS have been identified and adjusted for. Such techniques have been developed and further studies in recent years. (Turner et al., 2009; Thompson et al., 2010).

In some assessments, reviewers forego meta-analytical approaches and produce a narrative summary. A narrative summary involves the systematic organization and presentation of the data from primary studies. Data can be arranged based on certain aspects of interest, for example based on various combinations of technology components, subgroups of interest, etc, which can help the reviewer and consumer recognize themes across studies (Petticrew et al., 2013). This practice can potentially be misleading, however, as reviewers can choose to emphasize certain aspects over others, and, if possible, the organization of the narrative summary should be pre-specified, and where post-hoc organization is performed, this should be explicitly stated (Higgins & Green, 2011).

Information from individual studies can also be summarized and portrayed tabularly (Italia & Rehfuess 2012) or graphically. The harvest plot, a graphical method for presenting and summarizing evidence has also been shown to be useful in effectiveness assessments of complex technologies, especially where substantial heterogeneity is present and MA is deemed inappropriate or not feasible (Ogilvie et al., 2008; Turley et al., 2013).

Mixed method and qualitative approaches to evidence synthesis

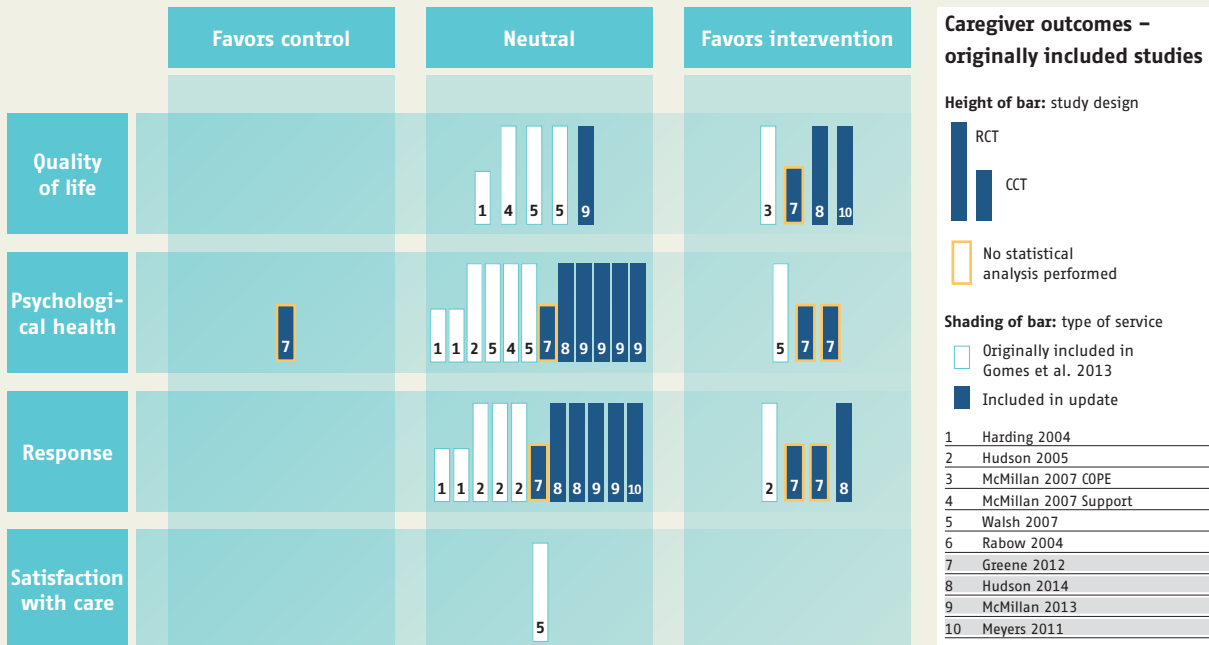
This guidance does not aim to provide in-depth instructions for applying qualitative and mixed methods approaches, but these have been well-described with examples, along with their relevance to reviews of complex technologies (Petticrew et al., 2013). For those working to ascertain the effectiveness of complex technologies it is important to recognize that certain broad questions related to the effectiveness, e.g. "Do those receiving or delivering the technology feel that it is effective?", "What parts of the technology could be improved?", may be best addressed through qualitative primary research, and thus at the secondary level through the incorporation of primary qualitative data into the evidence synthesis. This qualitative data may or may not then be integrated with quantitative data in a mixed methods approach. In the associated INTEGRATE-HTA case study, alongside the quantitative review assessing the effectiveness of reinforced home-based palliative care, a qualitative review was performed to identify enablers and barriers of context and implementation of home-based palliative care services in Europe (Brereton et al., 2016). The two reviews together could provide a rich resource for decision makers, helping them not only to define aspects of reinforced home-based care which may be effective, but also to identify specific enablers and barriers of context and implementation, if such a technology is to be implemented in another setting and context.

Box 4: From the INTEGRATE-HTA case study (Brereton et al., 2016)

In the associated case study on reinforced home-based palliative care, it was clear from previous similar systematic reviews and a scope of the newer literature that the identified primary studies would vary widely with regard to populations, technologies, comparators and outcomes. Based on this knowledge, it was decided at the protocol stage that the included comparisons would likely be too heterogeneous for a MA, and that harvest plots would be created instead.

Figure 3 shows the harvest plot including those outcomes important for lay caregivers, who care for patients receiving palliative care at home, but who also receive support to prevent and/or address the burden due to this care. Similar to the narrative summary, harvest plots can also be organized based on PICO aspects of interest or methodological differences, in order to investigate possible trends in effectiveness in subgroup and sensitivity analyses respectively. In Figure 3, for example, the study design is represented by the height of the bar, with NRS being represented by a shorter bar. If NRS were to systematically differ from RCTs in the effect measure, this would be visible on the harvest plot, and other methodological or clinical aspects can be investigated in this manner.

Figure 3: Harvest plot showing technology effects for lay caregiver outcomes, in review of reinforced home-based palliative care.



Inclusion of stakeholders in evidence synthesis process

In section 2.3.1 we highlighted how stakeholders can be involved in the scoping process, to ensure that the effectiveness assessment asks the right questions in the appropriate populations and against the appropriate outcomes, etc. Many bodies, including the Cochrane Collaboration and EUnetHTA recognize the importance and value in including various stakeholders and end-users in the review planning in this way (Cochrane Public Health; Core Model), and such practices only become more important with increasing complexity. Methods are also available, for example Interactive HTA, which promote the inclusion of various stakeholder perspectives throughout the evaluation of the technology (Reuzel et al., 2001). The active incorporation of stakeholders in the evidence synthesis is also possible. Several examples of the incorporation of expert opinion into Bayesian meta-analysis or other types of analyses exist (See et al., 2012; Woertman et al., 2013), and the potential use for the inclusi-

on of other various perspectives, including patients, has also been recognized (Facey et al., 2014).

The inclusion of various stakeholders at the evidence synthesis stage of the effectiveness assessment is rare, and further research should propose and evaluate methods of making this more accessible to those carrying out such assessments.

2.3.3 (Conditionally) specifying methods *a priori*

A scope of the evidence, preceding the actual searches, will only identify a fraction of the potentially relevant primary studies. An important question, emphasized by Schünemann et al. is, therefore, whether it is truly feasible to define methods *a priori* before the evidence to be synthesized has been identified (Schünemann et al., 2013). That paper deals only with the consideration of NRS for systematic reviews, but this thinking can be very well extended to include choosing an appropriate method

Box 5: From the INTEGRATE-HTA case study (Brereton et al., 2016)

As INTEGRATE-HTA emphasizes the importance of integrating perspectives of stakeholders into the HTA at various stages, we also developed a method for including expert input at the evidence synthesis stage, as part of the case study on reinforced home-based palliative care. The method, called post-review gap analysis with expert consultations, ensues only once the traditional evidence synthesis is completed. In the case study, as previously described, this entailed the creation of harvest plots to assess trends in effectiveness. Once this was completed, the review team performed a gap analysis of the harvest plots and identified evidence, as part of an open, group discussion, focusing on identifying potential knowledge gaps either not addressed by or arising during the effectiveness assessment. Based on topics identified in these discussions, we then consulted a small group of home-based palliative care researchers and professionals, with the goal of exploring the assessment results further and discussing the relevant research gaps. In the context of the gap analysis, the review team felt it most interesting and appropriate to discuss why the majority of the effects, as seen in the harvest plots in Figure 3 were neutral with regard to both patient and lay caregiver outcomes.

Of interest in the expert consultations was therefore, based on the knowledge and experience of each expert, what methodological or palliative care related issues may have contributed to, or in the future could help address the seemingly ineffectiveness of various reinforced home-based palliative care services. More on the methods and results can be found in.

for evidence synthesis. For some complex technologies, this question may be less relevant, and it may be quite clear to the reviewer before any searches are carried out, based on a scoping exercise as outlined above, that several direct randomized studies will be included, and that statistical pooling of the evidence will be appropriate. Similarly, the reviewer may know from scoping, that little randomized evidence exists or that it is strongly indirect, that NRS will be included, and that the evidence will be presented without attempting to statistically pool results. For such instances, methods for all stages of the review can and should be defined a priori at the protocol stage, and these should be applied in conducting the review. This is represented by the dark blue boxes in Figure 2, and in such an assessment, no further planning is necessary, and the review can carry on until conclusion.

For other complex technologies, a final decision regarding what types of evidence to include and the method of evidence synthesis to apply should perhaps be delayed until after the primary literature has been identified. The a priori specification of methods, however, lends the systematic review its methodological rigor, and a definition of methods only once the relevant evidence has been identified could threaten this. As outlined in Schünemann et al., in order to ensure the methodological rigor of the effectiveness assessment, the reviewer could

specify at the protocol stage a conditional set of methods, along with an alternative, and a rationale for deciding between the two (Schünemann, 2014).

A conditional specification of the method of evidence synthesis is not uncommon in published protocols of effectiveness reviews. The following statement, taken from a review protocol by Goudet et al., “Nutritional interventions for preventing stunting in children (0 to 5 years) living in urban slums” published by Cochrane Public Health mirrors that found in many reviews:

“We will consider heterogeneity by examining the study design, participants, setting, intervention duration and age group. If studies reporting the primary outcome are sufficiently similar, we will conduct a meta-analysis. When meta-analysis cannot be conducted, we will report the results in a narrative way” (Goudet et al., 2015).

Such a conditional decision regarding what types of study designs will be included, however, is less common. For assessments of complex technologies, where it may not be clear what types of study designs have been used to assess effectiveness, or what types of information the various study designs may contribute, this flexibility will help ensure that reviews include the best available evidence. The Cochrane Handbook does hint at the necessity of this practice in the chapter dedicated to the inclusion of NRS:

“The NRSMG recognizes that it may not be possible to pre-specify all decisions about the methods used in a review. Nevertheless, review authors should aim to make all decisions about the methods for the review without reference to the findings of primary studies, and report methodological decisions that had to be made or modified after collecting data about the study findings” (Higgins & Green, 2011).

The pre-specification of study designs to be included protects against review bias, and should therefore be performed where possible. A conditional specification of the types of evidence to be included with the possibility of altering this specification, however, need not be considered a methodological weakness, as it aims to provide decision makers with the best available and most useful evidence for informing decisions.

As outlined in Figure 2 and described throughout 2.3.1 and 2.3.2, in selecting study designs to be included and in deciding on a method for evidence synthesis, whether this selection is conditional or not, the reviewer should consider

- The specific research question and PICO of interest for the review, as well as the related complexity, as well as the state of the methodological and clinical evidence and
- The characteristics of available options for study design inclusion and various evidence synthesis methods.
- Thus, based on the question and sub-questions the reviewer wants to assess, on what evidence exists in what forms, and on the characteristics of potential methods, i.e. benefits and limitations, a decision can be made and methods specified.

At this stage, after the a priori specification of the methods for conducting the systematic review, the searches for and screening of relevant evidence can begin, and the following steps should take place after the initially identified records have been narrowed down to those studies, which will potentially be included in the review. If reviewers decide that a conditional specification of study designs to be included and method of evidence synthesis is most appropriate, meaning that these decisions may still be altered, it is extremely important that no studies are excluded based on study design. Such exclusion could result in the loss of a relevant study at a later stage if the list of included study designs is expanded.

2.3.4 Assessing of methodological and clinical heterogeneity

It was discussed in 2.3.2 that understanding the various sources of heterogeneity, as well as their influence on effectiveness may be of interest in evaluating complex technologies. The present discussion, however, is relevant for effectiveness assessments, in which reviewers decided to conditionally specify methods for study design inclusion and method of evidence synthesis at the protocol stage. This is represented by the light blue boxes in Figure 2. For such assessments, after a potential body of evidence has been identified through the searching and screening stages of the systematic review, sources of methodological and clinical heterogeneity must be examined in order to determine whether the conditionally specified methods are appropriate, or whether the reviewers should consider alternative methods.

Box 6: From the INTEGRATE-HTA case study (Brereton et al., 2016)

Boxes 2–5 describe, in the effectiveness assessment of reinforced home-based palliative care, how we fine-tuned the research question and the specific scope of the effectiveness review (Box 2), assessed the literature to determine what types of study designs would likely contain the relevant information (Box 3), and developed an overview of available methods (Box 4).

These steps allowed us to then decide to:

- Not statically combine results from primary studies through meta-analysis
- Create harvest plots based on the evidence (Box 4)
- Perform a post-review gap analysis followed by expert consultations with palliative care professionals (Box 5)

Heterogeneity and study design inclusion

As outlined in 2.3.2, in deciding between the appropriate study design inclusion criteria, the reviewer should consider 1.) how direct the evidence from various types of evidence is and 2.) the potential risk of bias introduced by these types of evidence. At this stage, where all potentially relevant evidence has been collected, the reviewer can assess the identified study designs based on these aspects, and decide whether the conditionally specified study designs to be included provide an evidence base which can be appropriately synthesized and provide decision makers with useful evidence for informing a decision. If the conditionally specified study designs do not provide sufficiently direct evidence, or introduce substantial risk of bias, then the reviewer should adapt accordingly. This could entail collecting additional types of evidence to complement, or alternative types of evidence to replace that which has been identified. For a detailed discussion of directness and risk of bias, the respective sections in 2.3.2 above should be consulted.

Heterogeneity and the method for evidence synthesis

Clinical and methodological heterogeneity have strong implications for the method of evidence synthesis, because 1.) they determine the appropriateness of statistical pooling, and 2.) for complex technologies aspects related to heterogeneity may be of interest for the review and potential decision makers. With all potentially relevant studies for inclusion at hand, the reviewer can now assess the conditionally specified method for evidence synthesis, and determine whether this method is appropriate for the present evidence base. If, for example, some form of meta-analysis is planned, yet studies assess a range of different PICO elements differently, e.g. children and adults included in different studies, several related yet fundamentally different technology assessed, outcomes measured using incomparable methods, etc., then statistical pooling may not be appropriate, and the alternatively specified method should be considered. If, in this same case, wide clinical heterogeneity had been expected, and harvest plots had thus been conditionally specified, then remaining with the conditionally specified harvest plot will likely be appropriate.

2.3.5 Specifying final decision on methods

At this stage, the reviewer has made a judgment about whether or not the conditionally defined study designs to be included and method for evidence synthesis are appropriate given the identified evidence base. Based on this judgment, the reviewer will decide either to apply these methods, or those specified as the alternative, and the review will thus be conducted as such.

2.4 CONCLUSIONS

2.4.1 Main insights for the assessment of complex technologies

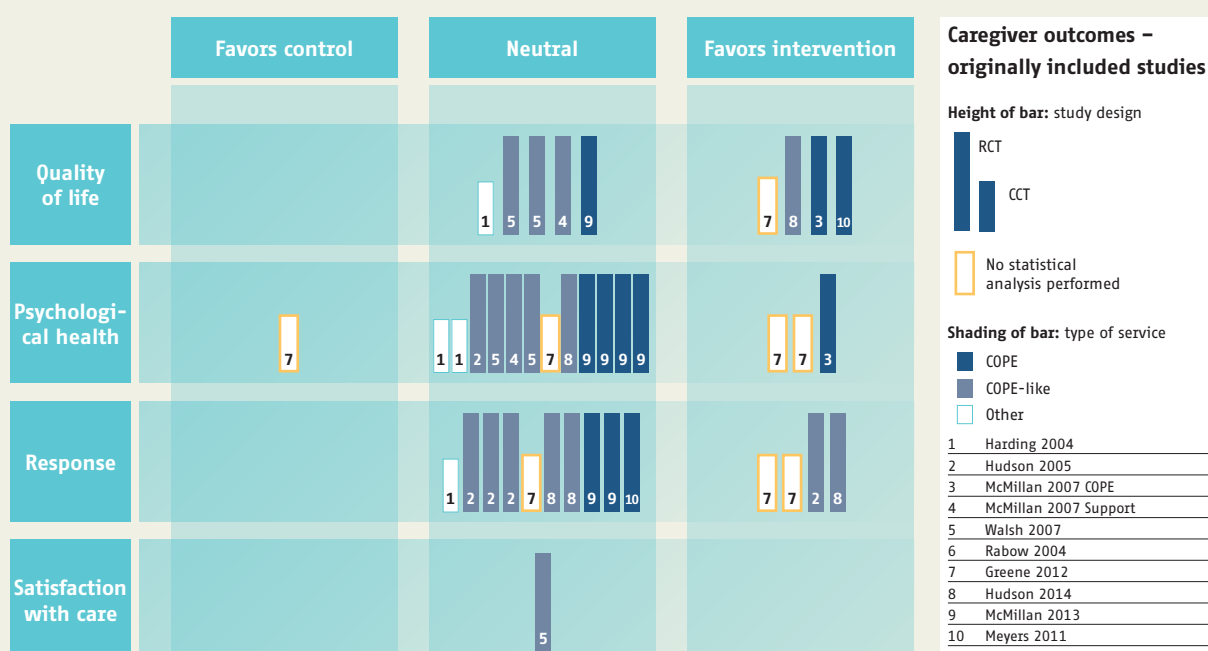
Technology complexity, as well as overall system complexity, has major implications for all stages of an effectiveness assessment, from defining the review question to the final stages of results interpretation. Such complexity has wide-reaching implications for deciding what types of evidence to include in the review and for deciding what method of evidence synthesis to apply, decisions which potentially greatly influence the results of the assessment. It is important, therefore, that reviewers consider this complexity from the beginning, when defining the review question and the PICO elements of interest. Assessing the effectiveness of various facets of complex technologies may require data from a variety of types of evidence, and choosing the appropriate type of evidence entails finding direct evidence addressing the research question, while monitoring and limiting bias introduced into the assessment. Deciding upon an appropriate method for evidence synthesis when assessing a complex technology requires an understanding of how various methods can help the reviewer address the research question, whether the question deals with overall effectiveness or with exploring and assessing heterogeneity in order to explain trends in effectiveness. In the presence of complexity, some flexibility with regard to method specification may allow reviewers to produce recommendations based on the most appropriate methods using the best available evidence. This, in turn, may help ensure that decision makers have the best effectiveness evidence to inform decisions. It is also emphasized that certain

Box 7: Supplement to the INTEGRATE-HTA case study

In the INTEGRATE-HTA case study (Brereton et al., 2016), we were unable to fully integrate these effect modifiers into the effectiveness assessment. The following, however, illustrates, in a post-hoc manner, how such important considerations can influence the effectiveness assessment.

The assessment of moderators of treatment outcome for caregivers caring for patients at home found some evidence pointing to the fact that caregiver competence had a positive effect on caregivers' feeling of manageability. Based on these results, we planned a post-hoc subgroup analysis. We hypothesized that those interventions providing caregivers with competences for caregiving may be more effective across caregiver outcomes than those simply treating the burden associated with caregiving. A subset of identified interventions included in the effectiveness assessment was designed to help caregivers develop skills and competencies for caregiving. For these interventions, known as COPE (Creativity, Optimism, Planning, and Expert Information) interventions, we performed a post-hoc subgroup analysis, creating a harvest plot portraying only the results of these studies compared with those from non-COPE intervention studies.

Figure 4: Harvest plot assessing whether effects for lay caregiver outcomes are better for COPE interventions compared to other interventions.



Visually comparing the COPE interventions, portrayed in black in Figure 3, with all other interventions, it would not appear that COPE interventions are more effective than other included interventions. This post-hoc subgroup analysis is, of course, based on a small pool of studies, and simple visual trends are assessed, thus interpretations should be very cautious.

Additionally, relevant context or implementation aspects could be assessed. The assessment of context identified evidence showing that whether reinforced home-based palliative care takes place in an urban or rural area may be an effect modifier. Based on this information, a subgroup analysis could be performed. Ideally, such subgroup analyses would be planned at the protocol stage, based on a priori hypotheses, which could emerge, from example, from the assessments of these potential moderators as described in related guidances (van Hoorn et al., 2016; Pfadenhauer et al., 2016).

Additionally, other methods of evidence synthesis, such as network meta-analysis, meta-regression and Bayesian meta-analysis, facilitate the statistical assessment of such trends in effectiveness, and may, therefore, be appropriate for such questions.

aspects such as patient preferences and moderators and predictors of treatment effect (van Hoorn et al., 2016), as well as context and implementation (Pfadenhauer et al., 2016) may act as effect modifiers and should also be considered at all stages, Box 7 below illustrates how such modifiers could inform the effectiveness assessment.

current state of the art, but it will be important that researchers continue to experiment, empirically test and improve methodology, and to ensure that effectiveness assessments provide ever more reliable and useful information for consumers.

2.4.2 Strengths and limitations of current method(s)

This guidance is not meant to provide comprehensive instructions for the entire effectiveness assessment process. Thus there are many stages of the review, e.g. searching, data extraction, risk of bias assessment, which are also highly influenced by complexity, yet these are not included in detail here, and users will have to look elsewhere for guidance on these stages of the review. Also much of the guidance development was based on two journal special issue series. These sources, however, may be considered state of the art for effectiveness reviews of complex technologies, and their use in informing the guidance was appropriate. Additionally, given that each effectiveness assessment of a complex technology will be somewhat unique, it is not possible to specify one set of methods that will perform well in all such assessments, meaning there is a limit to how specific such a guidance can be. In this guidance, however, a range of options for study design in inclusion and evidence synthesis are documented and described, and it is emphasized that the reviewer make decisions regarding these methods only after substantial consideration of the research question, the technology and the system in which the technology exists, the resulting a complexity and the existing evidence. The guidance also suggests that controlled flexibility in deciding upon methods may also be necessary to ensure that effectiveness assessments provide the best possible evidence for informing decisions.

2.4.3 Outlook

Much methodological progress has been made over the past decade in effectiveness assessments, especially as complex technologies are more often designed, implemented and evaluated. New research is also constantly underway related to including various types of heterogeneous evidence, and synthesizing this evidence. This guidance represents a fraction of the

3 GUIDANCE TO ASSESS ECONOMIC ASPECTS

By: James B. Chilcott, Sue Ward, Hazel Squires

3.1 INTRODUCTION

3.1.1 Purpose and scope of the guidance

Aim of this guidance

Complex interventions and particularly those that have the potential to interact with the context and setting of the health system within which they act throw up special problems in relation to health technology assessment and more specifically their health economic assessment.

The aim of this guidance is to provide recommendations for practice and future methodological research in health economic evaluations within HTA. The recommendations for practice focus on the use of systems approaches for capturing complexity in model based health economic evaluation.

How does this guidance relate to other guidance in the field?

This guidance does not seek to replace existing guidance for economic evaluation in HTA, but rather to sit alongside such guidance and expand on methods of particular relevance when considering complex interventions acting in a complex health system.

In recognition of the European context of the INTEGRATE-HTA project, this guidance takes as its particular starting point existing guidance on economic evaluation captured in the HTA Core model (European network for Health Technology Assessment - EUnetHTA).

The guidance is also developed with respect to current guidance from the European region as collated by the International Society for Outcomes Research (ISPOR) 'Pharmacoeconomic guidelines around the world' initiative (Eldessouki & Smith, 2012).

3.1.2 Background

Complexity science

The study of complex systems is the study of how relationships between parts of a system give rise to the collective behaviour of the system and how such a sys-

tem interacts with its environment. The central ideas in this study being ones of emergence, adaptation and interaction between the many agents that comprise a complex system. The science of complexity has the objective of understanding the properties of these systems; understanding which rules govern their behaviour? Understanding how such systems adapt to changing conditions? Understanding how they can learn efficiently and how they can optimize their behaviour?

Aspects of complexity in HTA and economic evaluation

With respect to HTA aspects of complexity are described in section 1.2.1, Table 1

Undertaking economic evaluations for complex interventions in complex systems raises a number of issues, ranging from lack of clarity regarding the exact nature of the intervention and the comparator, the potential need to deal with multiple outcomes and multiple perspectives within the economic evaluation, alongside challenges with estimating effectiveness from complex interventions (Husereau et al., 2014). 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. Shiell describes complex systems as being adaptive to their local environment, as behaving non-linearly and as being part of hierarchies of other complex systems (Shiell et al., 2008). Further consideration of these issues is needed, and, where feasible, additional guidance would be useful. Particular features of complex interventions in complex settings that impact on economic decision making include:

- ▶ number of groups or agents acting with intention in the system,
- ▶ number and nature of interactions between agents in the system,
- ▶ nature of control within the system,
- ▶ degree of variability in intention and response of agents in the system,
- ▶ potential for adaptive behaviour within the system,
- ▶ degree of flexibility and co-evolution of intervention and setting and
- ▶ degree of historicity, time and path dependence.

3.2 GUIDANCE DEVELOPMENT

3.2.1 Process of guidance development

The guidance has been developed according to the following process:

- ▶ A review of existing health economics guidance within HTA from the European region was undertaken and the guidance was assessed against the classification of aspects of complexity described in section 3.1.2 and with respect to literature from the complexity science and HTA domains. Issues relating to the relevance and appropriateness of existing guidance for the evaluation of complex interventions acting in a complex health setting are discussed and recommendations for practice and future research made.
- ▶ Guidance was developed on systems approaches to model based health economic evaluation for complex interventions in complex settings, based on the methodological literature on systems approaches. The guidance addresses the topics highlighted by the Recommendations for Practice in the review.
- ▶ The guidance was tested and further developed through implementation in a demonstration case study economic evaluation in reinforced home palliative care 'Integrated assessment of home based palliative care with and without reinforced caregiver support: A Demonstration HTA' methodological guidances' (Brereton et al. 2016)

3.2.2 Review of existing guidance on economic evaluation within HTA

The distinguishing feature of HTA and health economics within HTA, is its focus on using evidence to support healthcare decision / policy making. The review of health economic guidance therefore focused on guidance pertaining within the EU and issued by or relating to national policy making bodies. The review took a specific focus on countries directly involved in the INTEGRATE-HTA project namely, Norway (Norwegian Medicines Agency, 2012), Italy (Capri et al., 2001), Germany (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, 2009), Netherlands (College voor zorgverzekeringen, 2006), Poland (Task force for the preparation of guidelines for health technology assessment, 2009) and England (NICE, 2009; NICE, 2013). Guidance current in 2013 was included in the review.

The review focused on four themes coherent with the key economic elements within HTA described by the HTA Core Model:

- ▶ theoretical underpinning, health economics methodology and perspective,
- ▶ scoping and defining the decision problem,
- ▶ health and wellbeing outcomes and
- ▶ resources and costs.

Discussion relating to the four themes within the reviewed guidance was extracted. A full report of the review is presented in Appendix 9.1, this comprises a narrative critique of the guidance particularly with respect to the previously discussed aspects of complexity and with reference to the methodological complexity science literature. Recommendations for practice and future research are identified.

3.2.3 Conclusions of the review of existing economic guidance within HTA

Key characteristics of complexity, including the existence of multiple perspectives and the potential for adaptation and co-evolution are not addressed by the guidelines reviewed. Under these conditions assumptions underpinning traditional methods of economic analysis may not hold, for example assumptions regarding stationarity of the system. Furthermore traditional economic approaches aim at maximising a single economic objective function, such as population health (or total quality of life) subject to fixed resource constraints. Considerations of complexity may suggest a move away from such an optimisation paradigm to one of system improvement. Methods for assessing whether the complexity in an intervention/setting matters for economic evaluation are required. Methodological development is required to further understand the potential of computational complexity science methods for changing the role of health economics within HTA in supporting health policy making and the potential of such methods to provide a health economic framework that allows the role of adaptation, evolution and strategy playing in the health economic market should be investigated. Computational modelling techniques, such as agent based modelling and social network analysis may be useful for understanding the health economic impact of adaptive behaviour and co-evolutions of intervention and setting within HTA. Exploring methodologies to bring evaluation and decision making closer together may be helpful to resolve some of the issues raised by complexity within

economic evaluations. Further research into the modelling of behaviour within health economic models is required, along with the development of methods of economic evaluation aimed at supporting decision making in the context of rapidly developing definitions/taxonomies relating to resources and costs. Ongoing research into methods for measuring and valuing non-health benefits in situations of complexity and for incorporating them into the HTA processes will also be important.

3.3 HOW TO APPLY THE GUIDANCE

3.3.1 *Guidance recommendations for methodological research and practice in the economic evaluation of complex interventions in complex settings*

The following guidance includes recommendations for research and practice in the economic evaluation of complex interventions in complex settings. The recommendations are based upon a critical review of health economics guidance in HTA, on literature from the complexity sciences and on systems thinking. Appendix 9.1 provides a full report of the review and recommendations arising from the review. The recommendations here include the major recommendations reported in Appendix 9.1 and further developed through a demonstration case study economic evaluation in reinforced home palliative care (Brereton et al. 2016).

RECOMMENDATIONS FOR RESEARCH

RESEARCH RECOMMENDATION 1: Complex systems challenge the traditional role of HTA and specifically economic evaluation in HTA. Methodological development is required to further understand the potential of complexity science methods for changing the role of health economics within HTA in supporting health policy making.

Aspects of complexity including indeterminacy in definitions of interventions, comparators and outcomes, historicity and path dependence of intervention effects, the co-evolution of intervention and setting, including often rapidly developing technologies all challenge the generalisability of evidence and undermine the traditional methods of HTA and economic assessment.

Shiell et al. (2008) suggests that a possible response maybe to move towards a closer relationship between

evaluation and practice when considering complex interventions in complex settings. This has important implications including the necessity to collect economically relevant information as a part of practice evaluation and to ensure that economic criteria are relevant to micro and meso level decision making as well as the macro or policy level. Assessments that need to account for significant co-evolution between the intervention and the setting may need to incorporate methods of Health Service Research and Health Technology Assessment. Bringing economic evaluation research and practice closer would move health economics within HTA from a passive gate-keeping role, as implied by the binary 'yes/no' reimbursement framework, to playing an active role in shaping the development and definition of technologies that comprise the health system.

RESEARCH RECOMMENDATION 2: The potential of computational complexity science methods to provide a health economic framework that allows the role of adaptation, evolution and strategy playing in the health economic market should be investigated.

Health economics guidance and the supporting methodological literature frame the economic decision problem as one of maximising health outcomes from the expenditure of a fixed budget (Gold et al., 1996; Drummond et al., 2005). The solution encapsulated in the cost effectiveness acceptability threshold relies upon several strong assumptions, for example stationarity, equilibrium and perfect knowledge, complexity methodologies seek to relax these assumptions. Arthur (Arthur, 2013) therefore places traditional theoretical methodologies as special cases of the broader complexity methodologies.

The complexity science approach relies heavily on computation as a method for exploring the structure of a problem situation, for understanding the rules that govern a system, for theory building and for exploring ways to intervene in a system to promote desired outcomes. In contrast traditional health economic methods use computational simulation for generating probabilistic predictions of key economic outcomes. Methodological research is required to understand the implications of the complexity science approach for HTA and particularly health economic methods in HTA.

RESEARCH RECOMMENDATION 3: Continuing research into methods for measuring and valuing non-health benefits and appropriate methods for incorporating them into the HTA process is required.

Health care decision-making to date has typically focused on improvements in health and this has trans-

lated into the recommended use of the QALY within cost utility analysis (CUA). The benefits of interventions that seek to improve an individual's quality of life beyond health may not be adequately reflected within current HTA processes. For example, in the Public Health field there has been growing recognition that the objectives of many complex interventions are broader aspects of quality of life. These include non-health outcomes such as empowerment, participation, the ability to form or maintain friendships, feel safe or retain dignity and self-respect (Kelly, McDaid, Ludbrook, Powell in Coast et al., 2008). Additional issues are raised when considering the use of multiple outcome measures to inform resource allocation within and between the health care, social care and public health sectors. A recent review, aimed at stimulating research in this area, outlined a range of alternatives for addressing this issue, which fall into three broad categories: extending the QALY beyond health, using wellbeing to value outcomes and using money to value outcomes (Brazier & Tsuchiya, 2015). Methodological development in measuring and valuing health and non-health outcomes is an on-going agenda both in terms of expanding the domains of outcomes included and developing the methods of assessment.

RECOMMENDATIONS FOR PRACTICE

A systems approach provides a useful conceptual framework for assessing complex interventions in complex settings (Pitt, 2015; de Savigny & Adam, 2009). A systems approach is a holistic way of thinking about complex systems that focuses upon the interactions between entities and interactions between entities and their environment rather than assuming that a system can be understood by breaking it down into its individual components and studying each part separately. Within a systems approach, it is recognised that by considering one aspect of a system in isolation, there may be unintended consequences which, if ignored, may lead to perverse outcomes. The recommendations for practice presented here relate to specific aspects of such a systems approach.

A more detailed description of such a systems approach to HTA economic modelling is provided in section 3.3.2 of this guidance, which provides a modelling framework that expands upon and draws together the recommendations for practice. The system approach recommended here uses qualitative problem structuring methods for identifying and working with stakeholders to obtain a description of the complex system decision problem, together with quantitative model-

ling methods to generate predictive estimates of key economic outcomes to support decision making. The use of formal problem structuring methods aims to ensure the credibility, relevance and appropriate use of quantitative outcome predictions in supporting decision making.

PRACTICE RECOMMENDATION 1: A systematic consideration of stakeholders should be undertaken to ensure all relevant stakeholders are consulted.

Stakeholders should be involved throughout an economic assessment in a complex system. In order to avoid overlooking any relevant stakeholders it is recommended that stakeholders are classified into (a) people benefiting from the system (the customers), (b) the people performing the tasks in the system (the actors) and (c) the people with the power to approve or cancel the system (the owners). This should be done for both the health system that is the subject of the assessment and for the HTA economic modelling system itself. For instance within the health system the customers may be patients and carers etc and within the HTA system the customers may be the decision makers (e.g. policy makers, commissioners, clinicians, public etc). The relationships between the customers, actors and system owners should be explored in order to think about whether any relevant stakeholders have been missed. The economic modellers/analysts should, ideally, seek to engage representatives of each type, thereby ensuring all stakeholders views are taken into account.

PRACTICE RECOMMENDATION 2: An explicit process for identifying and prioritising research questions and defining the scope of assessment is an important component of a health economic analysis of interventions within complex systems. An iterative, consultative approach is proposed to ensure all stakeholder perspectives are captured.

The PICO (Population, Intervention, Comparator, Outcomes) framework is commonly used to structure the description of the scope of an economic evaluation. Aspects of complexity such as indeterminacy and multiple stakeholders present particular challenges in defining the PICO for complex interventions in complex systems. A broad understanding of the setting of the decision problem is required in order to make judgments about how well a PICO statement meets decision makers' requirements. This guidance recommends a consultative and iterative approach to obtaining an explicit description of the decision problem and scope. The starting point is to use a systems approach to build

on the formal consideration of the multiple stakeholders in the system (customers, actors and owners), by considering the location of decision making in the system and decision making perspectives of stakeholders. INTEGRATE-HTA guidance on logic modelling can be used to think about broader aspects of the scope and economic decision problem (Rohwer et al. 2016)

PRACTICE RECOMMENDATION 3: A formal consideration of aspects of complexity in the decision problem should be undertaken as part of the problem structuring activities.

The formal consideration of aspects of complexity involves describing: multiple and changing stakeholders and perspectives, indeterminate phenomena, uncertain causality, unpredictable outcomes and historicity, time and path dependence within the decision problem. This description should be developed on the basis of the initial immersion in the evidence and engagement with stakeholders and updated throughout the problem structuring activities. This explicit description of the aspects of complexity in the decision problem contributes throughout the economic modelling, including the definition of the decision problem, the problem and design oriented conceptual modelling and importantly in ensuring a correct interpretation of the quantitative modelling in the decision making process.

Using a systematic approach to defining potential causal pathways within the system, including positive and negative feedback, allows the nature of interactions within the system to be clearly defined. Methods for identifying and investigating the potential for adaptive behaviour within a system, the potential for co-evolution of an intervention and its setting, or indeed the impact of historicity and path dependence are areas for further research

PRACTICE RECOMMENDATION 4: The use of a systems approach to describe the intervention, setting, the agents and interacting components is recommended in order to provide a comprehensive understanding of perspectives and all the relevant outcomes.

Outcomes throughout the health care system will need to be explored and taken into consideration, as interactions at the local level may well impact on other elements within the health care system. The use of a systems approach to develop the economic model facilitates thinking about the interactions between parts within a system and with its environment (Squires, 2014), offering a means of exploring and defining the important relevant outcomes within the entire

system. It is likely to be overly simplistic to work on the basis that a system can be understood by breaking it down into its individual entities and studying each part separately. By considering the system as a whole, unintended consequences are less likely to be missed.

PRACTICE RECOMMENDATION 5: In considering complex interventions, the potential relevance of a broad range of health and wellbeing effects needs to be assessed. The implications of gaps in the evidence base on outcomes should be clearly highlighted

Health care decision-making to date has typically focused on improvements in health and this has translated into the recommended use of the QALY within cost utility analysis (CUA). This is most appropriate when the main or only benefit is a health benefit. Complex interventions may, however, impact on an individual's quality of life beyond health. Examples from the public health field include non-health outcomes such as empowerment, participation, the ability to form or maintain friendships, feel safe or retain dignity and self-respect. Methods for measuring these broader outcomes and including them in the HTA process are not, however, fully developed and therefore some of these outcomes may not be available for decision making. Explicit recognition of any important outcomes which are missing from the current evidence base is needed and the potential implications of these gaps in the evidence should be clearly presented within the decision making process.

PRACTICE RECOMMENDATION 6: Explicit choices made relating to inclusion of complex aspects of the decision problem within the quantitative model should be clearly documented to ensure that the outputs of the model are interpreted correctly.

When specifying the quantitative model there is a central design choice concerning whether and how to include complex aspects within the quantitative model or whether to consciously simplify the model and be clear about its applicability (See Practice Recommendation 3). This choice concerning the complexity of the model needs to take into account a number of factors, including the potential impact of complexity on economic outcomes, the evidence available, the time, resources and skills available to capture the complex aspects with the model and the purpose and role of the quantitative model in supporting decision making. Where decisions are taken to exclude complex aspects of the decision problem from the quantitative model, these decisions need to be clearly documented to ensure that the outputs of the model and

their potential limitations are clearly understood by the decision makers. Thus, for example it may only be feasible to generate a very simple model of a complex situation, whilst such a model may not be fit for the purpose of estimating cost effectiveness for a simple commissioning decision, nonetheless it may be sufficient to provide useful information for decision makers particularly with regard to designing intervention evaluations.

PRACTICE RECOMMENDATION 7: In considering the economics of complex interventions in complex settings, there is likely to be a range of outcomes which are potentially relevant. Where agents have different perspectives on outcomes, it may be important to retain a disaggregation of outcomes and there is likely to be an increased role for cost consequence analysis (CCA) to support decision making.

Where multiple agencies are involved in the delivery of a complex intervention or where the impact of the interventions falls across multiple agencies there is likely to be a range of cost, resource, health and wellbeing and other outcomes which are potentially relevant. Consideration will need to be given to how these will be presented and/or combined to support decision making. Consideration of a broad set of outcome measures will assist, at a commissioning level, to manage the introduction of a complex intervention into the health care system. Cost shifting between agencies within the system may act as a barrier to implementation of an intervention or may introduce perverse incentives. A systems approach is recommended for identifying the potential economic inter-relationships within the system and multi-agency cost consequence analysis is recommended to highlight the distribution of effects across the system and allow potential economic barriers and perverse incentives to be managed.

PRACTICE RECOMMENDATION 8: Economic evaluations of complex interventions in complex settings should explicitly consider translation of findings between contexts and settings and the limits of their applicability.

A defining characteristic of complex interventions in complex settings is that they may be unrepeatable and are setting or context specific. Reports of economic evaluations of complex interventions in complex settings should, therefore, give an explicit consideration to the limits of generalizability and translation between settings or setting specific analyses.

3.3.2 Applying the recommendations for practice: A systems approach for development of health economic models for complex interventions in complex settings

The recommendations for practice can be adopted as part of systems approach for undertaking health economic modelling. This approach is outlined in more detail in this section. The approach is based on a combination of problem structuring methods and quantitative modelling. Problem structuring methods are specifically designed to tackle complex problem situations where multiple potentially competing human perspectives are at play (Rosenhead & Mingers 2009). Whilst quantitative modelling has the benefit of enabling estimates of important outcomes to be generated subject to explicit and transparent assumptions. (Buxton et al., 1997) This approach therefore comprises a multi-methodology (Mingers & Gill, 1997) and is in line with good practice guidelines on conceptual modelling in health economics, and recent discussions regarding the use of systems approaches in assessing complex interventions (Husereau et al., 2014; Pitt et al., 2015; Roberts et al., 2012). The approach put forward draws upon research undertaken at the University of Sheffield focussing on the HTA modelling process, the modelling of whole disease systems and the modelling of complex public health systems (Squires, 2014; Tappenden, 2011; Chilcott et al., 2010).

The approach seeks to provide a methodology rather than a method, thus there is expected to be significant flexibility in implementation, with design choices necessary in adapting the implementation of the guidance to specific decision making contexts. It therefore relies on the skills of the economic modeller and requires the use of choice and judgement at a number of stages along the way. The application of the recommendations for practice described in this section aims to be a starting point for further development.

The systems approach - the HTA economic modelling system

The HTA economic modelling system is described in Figure 5. Step 1: identifying stakeholders and Step 2: aligning the process with the decision problem involve two external activities which are important to the model development process. Stakeholders input

should be sought at stages throughout the project. Aligning the process with the decision problem involves subjecting the modelling process to management and control to ensure that the process meets the required objectives of the project within the necessary constraints.

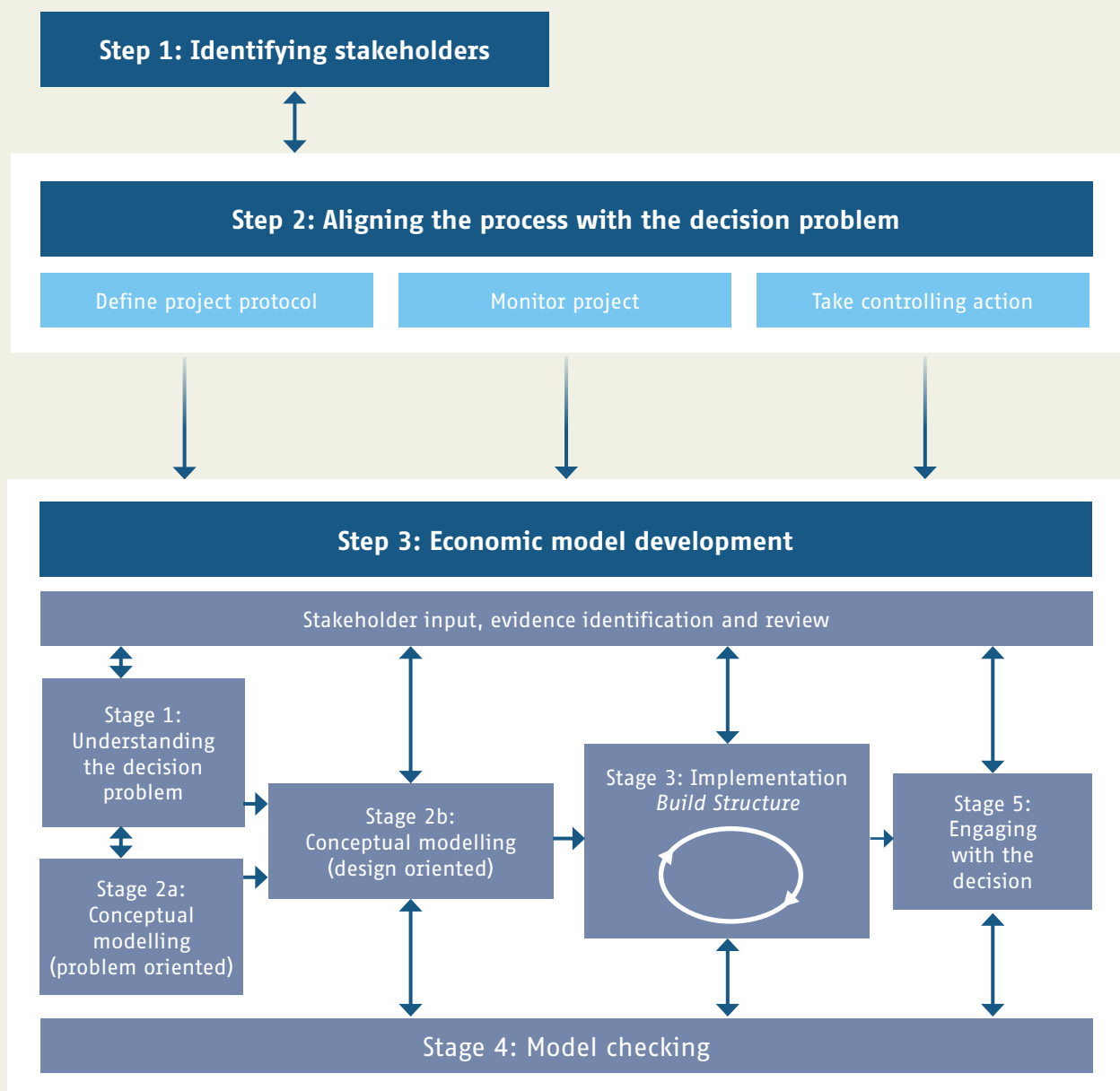
Step 3: the economic model development process has previously been described in terms of a five stage HTA modelling process for undertaking model based economic evaluations (Tappenden et al., 2012). This process is considered to be appropriate for the economic modelling of complex interventions and is used as the basis for the systems approach presented in Figure 5 with key modifications to ensure aspects of complexity

in the decision problem are addressed.

The five stages of the modelling process are:

1. Understanding the decision problem
2. Conceptual modelling
 - a. Problem oriented
 - b. Design oriented
3. Model implementation
4. Model checking
5. Engaging with the decision problem

Figure 5: The HTA economic modelling system.



These five stages should be undertaken sequentially, but with a high degree of iteration and linkage between the activities. Informing and shaping these modelling activities is a continuous process of engagement with stakeholders and evidence gathering activities. (Kaltenthaler et al., 2011)

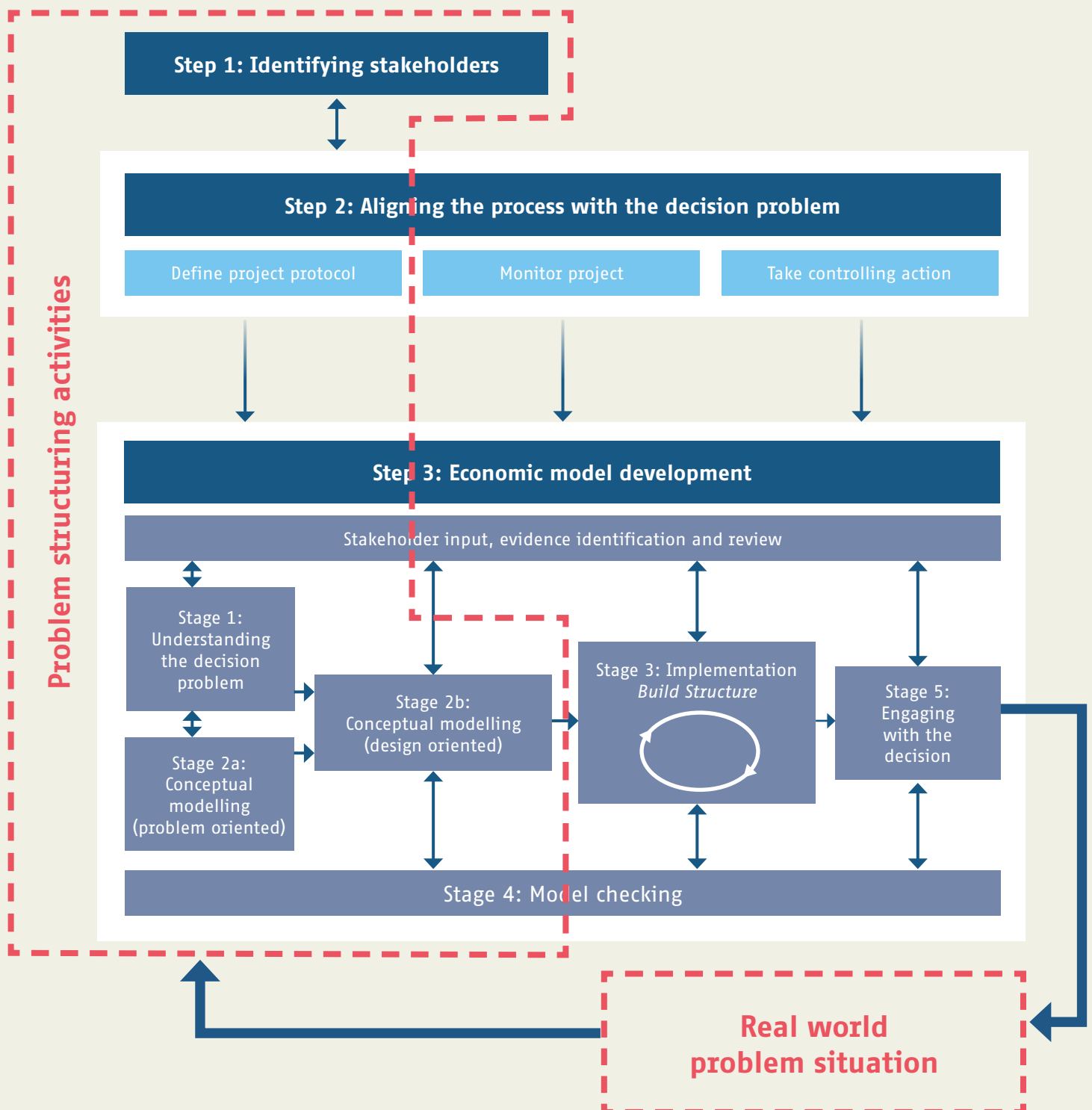
The stages described in this modelling system are broadly grouped into 'problem structuring', 'model implementation' and 'engaging with the decision'.

Problem structuring activities

The following problem structuring activities should be undertaken, as shown in Figure 6:

- identifying the stakeholders (Step 1),
- aligning the process with the decision problem (Step 2),
- understanding the decision problem (Step 3: Stage 1) and
- conceptual modelling (Step 3: Stage 2)

Figure 6: Problem structuring activities.



There is a high degree of linkage between these activities and they are all essentially conceptual in approach, the guidance here also draws upon Squires conceptual modelling framework for developing the structure of public health economic models (Squires, 2014).

Steps 1 and 2

The first two steps, identifying stakeholders and aligning the process with the decision problem, will generally need to be undertaken in parallel because the choice of stakeholders will impact on the fundamental definition of the decision problem. The selection of stakeholders may have a substantial impact upon the process and it may be necessary to iterate between choosing relevant stakeholders and developing the understanding of the problem since the understanding of the problem step may highlight the need to include stakeholders with specific expertise.

Step 1: Identifying stakeholders

KEY DELIVERABLE: formation of an Advisory Stakeholder Group for the economic evaluation.

It is recommended that an iterative, consultative approach is taken at all stages of economic model development. Stakeholders should be involved throughout the project, from the understanding of the problem stage and the conceptual modelling stage to engaging with the decision. An Advisory Stakeholder Group should be created.

The range of expertise that should be captured within the Advisory Stakeholder Group needs careful consideration. There are typically a range of different stakeholder types relevant when considering complex interventions in complex settings including for example clinical experts, public health experts, commissioning bodies, policy makers and lay members, all of whom

provide different expertise and bring different economic perspectives of the problem. The choice of stakeholders will inevitably affect the model developed and the interventions assessed. For instance, stakeholders help define the model scope, make value judgements, use their expertise to inform structural assumptions such as extrapolating short term trial data over the long term, and which interventions to assess within the model. These will be affected by what is considered to be culturally and politically acceptable, which is entirely appropriate in order for the model to be useful, but this highlights the necessity to obtain input from a range of stakeholders.

Few discussions of economic modelling methods to date have formally considered the range of expertise needed. Roberts et al. suggest that clinical, epidemiologic, policy and methods experts should be consulted, as well as patient representatives. (Roberts et al., 2012) A defining characteristic of complex systems is that they involve multiple agencies with multiple perspectives, this guidance therefore refers to methodologies developed explicitly for working in such contexts including Checkland's Soft Systems Methodology (SSM) (Checkland & Scholes, 1999) and Squires (Squires, 2014).

It is recommended that stakeholders are classified into people benefiting from the system (the customers), the people performing the tasks in the system (the actors) and the people with the power to approve or cancel the system (the owners). The economic modellers/analysts should seek to engage representatives of each type, thereby ensuring relevant stakeholders are not overlooked.

As well as describing the HTA economic modelling process as a system, a similar approach can be used to understanding and describing the problem situation that is the subject of the HTA. Thus we have two interacting systems at play; the HTA project and the health system that is the subject of the assessment, Table 5 be-

Table 5: Stakeholders as customers, actors and owners.

Stakeholder type	The subject system	The HTA system
Customers	People, patients, carers etc.	Decision makers, for example policy makers, commissioners, clinicians, public, industry.
Actors	People involved in the delivery of the intervention, people involved in the system within which the intervention acts.	Assessment team, stakeholder group.
Owners	Commissioners of the intervention and system within the intervention acts	Commissioners of the HTA

Box 8: Stakeholders in the reinforced palliative home care INTEGRATE-HTA case study (Brereton et al., 2016)

Table 6 classifies the stakeholders relevant to consideration of the economics of reinforced carer support interventions in home palliative care. This classification arose from initial reviews of the economic evidence base and was considered at the first economics advisory group workshop in the palliative care case study

Table 6: Stakeholders in the reinforced palliative home care case study.

Stakeholder	System	The palliative care system (ie subject system)	The case study HTA system
Customers (i.e. those that benefit)		Patients and carers	Decision makers: Policy makers, commissioners, clinicians, public, industry.
Actors (i.e. those that implement or are affected by the intervention)		People involved in the delivery of the intervention, i.e. reinforced carer support Healthcare professionals (NHS): MDT including OT, aromatherapy, etc Nurse (RA) Part time care advisors People involved in the system within which the intervention acts: Carers • Healthcare professional (NHS) - Primary care - Secondary care • Healthcare professional (Other) • Social care workers	INTEGRATE Assessment team, Contributors to the palliative care case study, Expert steering group Stakeholder Advisory Panel (SAP) group
Owners (i.e.those that decide to implement the intervention or not)		Commissioners of the reinforcement intervention? Commissioners of system within which the intervention acts? Cancer Commissioning Group (CCG)? Local Authority?	INTEGRATE Steering group EU commissioners of the HTA

low describes the stakeholders in each system. The relationships between the customers, actors and system owners should be explored in order to think about whether any relevant stakeholders have been missed.

Use of this classification to ensure a systematic consideration of potentially relevant stakeholders allows effective targeting of HTA economic evaluation, for instance where the customers for the economic evaluation are the owners of the subject system this allows a clear specification of economic outcomes of interest. Box 8 provides an example classification of stakeholders from the demonstration case study economic evaluation of reinforced carer support in palliative home care (Brereton et al., 2016).

Step 2: Aligning the process with the decision problem

KEY DELIVERABLE: the project protocol

The aim of Step 2 is to ensure that the modelling exercise meets the project requirements and abides by project constraints including resource and time, but also in the light of other political, context and environmental constraints. The HTA economic modelling system in Figure 5 describes a generic approach to the model development process which will need to be adapted to meet the requirements of each specific project.

A project protocol document should be developed to capture the initial outline of the project, as a basis for discussion between the project team and stakeholders. This

helps the clients to understand whether the project is planned to run appropriately and the project team with project planning. Key process decisions to be made during this step relate to the relevant modes of stakeholder engagement, the approach to evidence searching, and the time and resources available for the modelling project and each step of the modelling activity.

This protocol can then be used as the basis for ongoing monitoring and management of the project to ensure that the project can be delivered successfully, responding appropriately to any changes in circumstances throughout its course.

Step 3

Step 3 describes the economic model development process, with special consideration given to aspects of complexity

Step 3 Stage 1 : Understanding the decision problem

KEY DELIVERABLE: The 'understanding of the decision problem' for the economic analysis should be captured in a scope document

The first stage in the economic modelling exercise is to develop an explicit understanding of the decision problem that captures the views and perspectives of the different stakeholders. It takes as its starting point Step 1 of the INTEGRATE-HTA Model (Wahlster et al., 2016) in which the HTA objective is defined and preliminary definitions of the technologies of interest are presented, along with the specific logic model, the a priori model (Rohwer et al., 2016), generated for the technology of interest. This stage is involved with describing who will use the outputs of the economic modelling, the economic question to be addressed and should seek to identify specific interventions for assessment, if these have not been previously specified. The use of a systems approach assists in developing an understanding of the decision problem and scope for economic evaluation, based on an iterative, consultative process. The key deliverable of this activity is the scope of the economic modelling assessment.

There are two essential activities for the economic modeller/analyst at this point, engagement with stakeholders and decision makers and immersion in the evidence.

A key question to be addressed at the outset is whether the economic research question is best framed formatively or summatively. The choice is dependent on the decision making context and the complexity of the system. The decision maker may already have a scope that identifies specific interventions for assessment, similarly the decision making

framework and criteria may be well understood. In these cases and for many technologies, the relevant decision may be a simple binary commission / don't commission decision, in such cases the research question may appropriately be framed summatively as "What is the effectiveness and cost effectiveness of intervention A compared to B".

In some cases, however, the question may be better framed formatively such as "How should intervention A be implemented to ensure effectiveness and efficiency in practice". For instance where the complexity of an intervention allows for significant flexibility in implementation, or where the decision maker is only aware of the problem situation and requires the identification and/ or formulation of potential interventions.

A formal consideration of the aspects of complexity on the basis of the initial immersion in the evidence and engagement with stakeholders should be undertaken to help make this choice. This could be undertaken in a number of ways, but as a minimum would involve describing:

- ▶ Multiple and changing perspectives
- ▶ Indeterminate phenomena
- ▶ Uncertain causality
- ▶ Unpredictable outcomes
- ▶ Historicity, time and path dependence

Complexity may stem from stakeholders with conflicting perspectives, in these cases it may sufficient to identify economic transfers between stakeholders sufficient to resolve conflicts or it may be necessary to consider redesigning the system or identifying novel interventions that have the potential to be mutually economically acceptable.

Indeterminate phenomena, uncertain causality, unpredictable outcomes and historicity necessarily undermine the generalisability of the evidence base regarding costs and effects. For instance, in cases where an intervention or condition cannot be strictly defined it is very difficult to either synthesise existing evidence or indeed to generalise from that evidence to the problem situation under consideration. Similarly where there is a high degree of historicity, that is where the system is evolving rapidly, the conditions under which the available evidence base may have been generated may no longer appertain, again the direct relevance of the evidence base will be undermined.

In these cases a formative approach may be preferable that allows a common understanding and interpretation of evidence to be generated by stakeholders and specifically allows stakeholders to understand the relevance of the economic evidence base to their setting.

The formal consideration of the aspects of complexity should be developed on the basis of the initial immersion in the evidence and engagement with stakeholders and updated throughout the problem structuring activities. This explicit description of the aspects of complexity in the decision problem contributes throughout the economic modelling; it can be used to inform a judgement about whether complexity within the system or intervention matters for the evaluation, the definition of the decision problem, the problem and design oriented conceptual modelling and importantly in ensuring a correct interpretation of the quantitative modelling in the decision making process. Box 9 provides an example table describing aspects of complexity in the demonstration INTEGRATE-HTA case study of reinforced carer support in palliative home care (Brereton et al., 2016).

The 'understanding of the problem' should aim to identify a number of important elements:

- ▶ The economic research question, including intervention descriptions where appropriate.
- ▶ Decision making context
- ▶ Definition of the stakeholders and roles
- ▶ Population, Interventions, Comparators, Outcomes (PICO)
- ▶ Underlying theories

This 'understanding of the decision problem' should be captured in a scope document, but may also involve the development of a conceptual framework for the assessment. Developing an understanding of the decision problem is therefore an iterative process involving stakeholders and the assessment team undertaking initial broadly scoped searches of the evidence. Where the scope is not clearly definable at the outset a process that combines stakeholder based problem oriented conceptual modelling activities may be used in order to clarify understanding and develop a shared perception of the structure of the decision problem. There is significant flexibility in how this is done and the process may involve formal or informal methods in a facilitative environment. (Roberts et al., 2012, Tappenden et al., 2012) Insofar as formal methods such as cognitive mapping are used, this part of the process may overlap significantly with the problem oriented conceptual modelling activities described below. The NICE PH process and methods guidance (NICE, 2009) gives an example of such an iterative process including the use of realist methods of synthesis (Pawson, 2006).

The perspective and the key outcomes of interest for each of the stakeholders identified in the system that is the subject of the HTA - the customers (eg patients), actors (eg healthcare professionals) and problem owners (eg healthcare commissioners) - need to be clearly defined during this stage.

The outcomes identified at this stage constitute the decision making criteria for examination in Stage 5: Engaging with the decision problem.

Step 3 -Stage 2a : Problem oriented conceptual modelling

KEY DELIVERABLE : A written description of the health system (including social care and beyond) that describes the impact of the intervention(s) on economically relevant outcomes and description of the activities, services and resources within the system, identifying actors involved in the delivery of the intervention(s) and in the system impacted on by the intervention.

The aim of the problem oriented conceptual modelling stage is to develop explicit descriptions of the health system (which may include social care and beyond) that enable the potential impact of the intervention(s) on economically relevant outcomes to be made explicit and that enable judgements about the design of a model to produce quantitative estimates of these outcomes. Once again the logic model developed for the technology of interest in the INTEGRATE-HTA model (Wahlster et al., 2016) provides a starting point for this process.

There is flexibility in the conceptual modelling methods to be employed and the scope of the conceptual models considered. Two conceptual models are suggested:

- 1) The health and wellbeing logic model
- 2) The resource pathway model

The health and wellbeing logic model

The health and wellbeing logic model comprises a description of the causal pathway (proven or hypothetical) by which the health system is thought to contribute to the health and wellbeing and economic objectives of the patients and the healthcare system. Where a formative assessment is required this causal model can be used to identify potential interventions for assessment or provide the framework for a formative assessment of a problem situation (i.e. enable 'understanding of the decision problem'). This conceptual map can be used to identify the explicit value proposition for intervention, that is to identify the theory underpinning the intervention and identify how the intervention is thought to impact on economic and health and wellbeing outcomes.

Outcomes throughout the health care system will need to be explored and taken into consideration, as interactions at the local level may well impact on other elements within the health care system. Typically the main focus in HTA is on patient outcomes; outcomes of other agents may be parti-

Box 9: Aspects of complexity in the reinforced palliative home care INTEGRATE-HTA case study (Breton et al., 2016)

Table 7 gives examples of the aspects of complexity relevant to the economics of reinforced carer support interventions in models of home palliative care arising from the initial reviews of the economic evidence base and the stakeholder engagements in the palliative care case study.

Table 7: Aspects of complexity in the reinforced palliative home care case study.

Complexity	Reinforced palliative home care examples
1 Multiple perspectives	<p>The economic stakeholders will have differing perspectives related to goals and outcomes. They include:</p> <p>Customers: Patients, carers and families. Though palliative care engages with these holistically each will have different perspectives.</p> <p>Actors: Health and social care professionals, people working in the charitable and voluntary sectors.</p> <p>Owners: Local and national health and social care managers and policy makers, charitable and voluntary sector managers and policy makers.</p>
2 Indeterminate phenomena	<p>The philosophy of individualised palliative care, responding to patient & caregiver preferences means that interventions should be flexible & tailored to individual need. Needs and preferences will change over time as the end of life (EOL) phase approaches.</p> <p>Home based palliative care is not one single clearly defined/delimited intervention; it has been described as a “nexus of services around a patient”. A clear definition of the target population is lacking in terms of a) underlying disease, b) functional status, capability or need and c) time of referral within the disease trajectory, i.e. early or late. Similarly reinforced carer support is not a single well defined intervention and may contain elements of support that are routinely provided within conventional care (e.g. informal training/education of carers).</p> <p>Service goals are indeterminate: stakeholders discussed equity (reinforced carer support interventions should be offered to all) vs efficiency (interventions targeted at those in greatest need or with the greatest potential to benefit).</p>
3 Uncertain causality	<p>The COPE intervention, selected as the focus of the economic analysis was unique in having an explicit underpinning theory. However complexity of context makes the interpretation of empirical evidence base difficult; even well designed trials have difficulty determining causality.</p> <p>Care providers from a range of agencies work with patients with different diseases/ illness trajectories, any combination of which may interact differently with the causal chain of the intervention e.g. the COPE intervention demonstrates some effects in cancer patients, but no effect for Chronic Heart Failure patients, possibly due to the longer disease natural history meaning that patients and carers may already have developed coping strategies, reducing the potential impact of COPE at the EOL.</p> <p>Additional difficulties for evaluation, include ethical concerns about manipulating interventions considered to be beneficial to patients along with pragmatic problems of recruitment, attrition, missing data etc.</p>
4 Unpredictable outcomes	<p>There has been a lack of consistency with regard to which outcomes should be measured at EOL and the tools used to do this. There is some convergence in terms of outcome measurement tools, (e.g. OACC suite, AKPS, VOC, Zarit and IPOS) but outcomes continue to cover a broad range of domains. These outcomes do not translate into the single utility outcomes preferred by health economists to support traditional resource allocation decision making.</p> <p>There is uncertainty about which outcomes are most appropriate for the wide range of stakeholders, and how to balance these, especially if they are conflicting.</p>
5 Historicity, time and path dependence	<p>The practice of palliative care has changed over time and the philosophy of individualised care limits the generalizability and repeatability of an intervention.</p> <p>Changes to the palliative care system may impact on intervention effectiveness. The introduction of the ‘GP Contract’ in England in 2003/4 removed GP’s 24hr responsibility for the patient, the move towards District Nurses providing a task based service, the removal of medical paternalism and ‘putting the patient in control’ all impact on economics of the care system. Funding structures have a major impact on the provision of services and remain subject to ongoing reform. These interconnected dynamics would all potentially moderate the economic impacts of intervention, e.g. by affecting the ability of carers to divert patients from avoidable admissions to hospital or impact on the level of nursing care required.</p> <p>The Liverpool Care Pathway (LCP) demonstrated an extreme example of historicity. In the UK, even though the LCP initiative had operated effectively in a community setting, difficulties were experienced in the acute sector. Although the LCP has been abandoned in the UK, it has been adopted in other countries across Europe with a different historical pathway.</p> <p>The extent of these dynamic aspects would vary even throughout the UK; internationally the palliative care systems would potentially commence from very different starting points.</p>

cularly important in certain cases, for instance carers in the context of palliative care or families in the context of children's health. The potential relevance of broader health and wellbeing effects should also be considered, and included where justified. Examples include non-health outcomes such as empowerment, participation, the ability to form or maintain friendships, feel safe or retain dignity and self-respect. In a complex setting in which different agents have a different perspective on outcomes, it may be important to retain a disaggregation of multiple outcomes.

Box 10 provides an example health and wellbeing logic model taken from the demonstration INTEGRATE-HTA case study of reinforced carer support in palliative home care (Brereton et al., 2016).

The resource pathway model

The activity/resource model is a descriptive model of the activities, services and resources within the system, identifying actors involved in the delivery of the intervention(s) and in the system impacted on by the intervention. The focus of this description should be to identify the potential marginal impact of the intervention on resource usage, and therefore a description of current service provision is required. Kaltenthaler et al. suggest developing a service-pathway model which is a diagram of the treatment pathways of the population being considered. (Kaltenthaler et al., 2011) This model should seek to identify the direct resource impact of the intervention and the knock on impacts on the wider system.

The activity resource model needs to consider those aspects of complexity identified in developing the understanding of the decision problem. For instance, particularly where an intervention is multi-agency, these effects may extend beyond the healthcare domain. In considering the potential of the system to adapt in response to intervention, a decision needs to be taken with regard to the scope of the resource model. A minimum starting point is to identify the type of resources engaged in care or implied by the health and wellbeing logic model. The specific purpose of this is to provide a basis for justifying the resources and costs to be included in the design oriented model structuring stage.

The development of these conceptual models will allow definition of the complex information requirements for the project. Fulfilling these requirements will require evidence from a range of sources including the project scope, literature and stakeholder input.

The deliverable of this activity is a written description of the health system (including social care and beyond) that describes the impact of the intervention(s) on economically relevant outcomes and description of the activities, services and resources within the system, identifying actors involved in the delivery of the intervention(s) and in the system impacted on by the intervention. This should be shared with stakeholders to obtain feedback and verification. These descriptions allow the economic modeller/analyst to make and justify judgments about the design of a model to produce quantitative estimates of these outcomes.

Methods for 'understanding the decision problem' and 'problem oriented conceptual modelling'

This section gives a brief overview of two of the most commonly used Problem Structuring Methods (PSMs) which can potentially be employed to improve the understanding of complex decision problems (Franco, 2006). The economic modeller will need to select the most appropriate method.

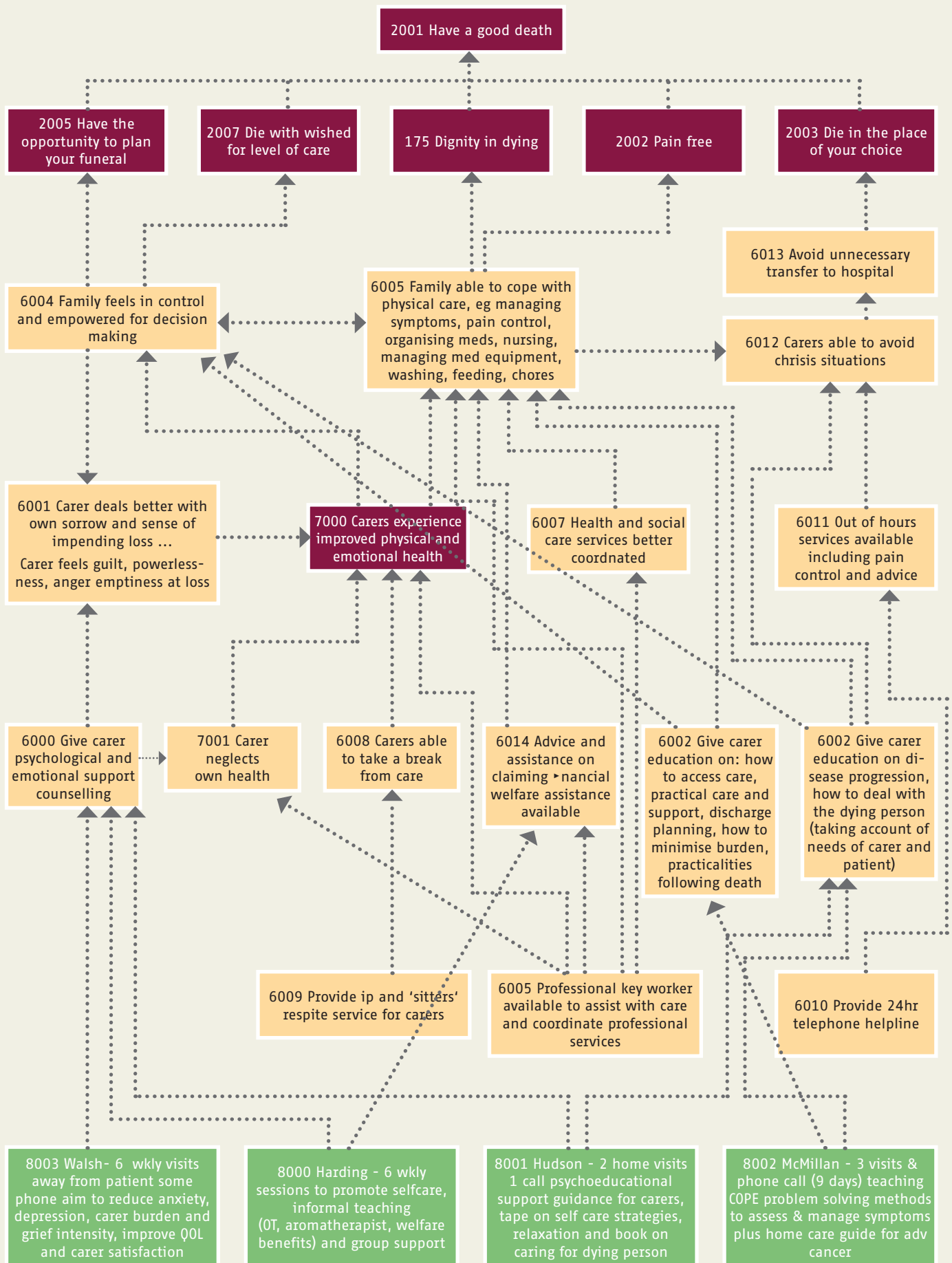
Squires reports a comparative assessment of the characteristics of PSMs including of Soft Systems Methodology (SSM), Strategic Options Decision Analysis (SODA) / cognitive mapping and causal diagrams. (Squires, 2014) A fuller account of these methods is available in the wider literature, with a useful overview being provided by Rosenhead & Mingers (2009). To demonstrate their potential SSM and cognitive mapping are outlined.

Briefly SSM provides a systematic approach for participants to share and learn about the world views of those involved. This process of learning is the means by which solutions can be generated, specifically solutions that can be accommodated by the different participants and have the potential to be successful. It's a methodology that employs system ideas to conceptualise and interrogate the structure of problems. It's an interpretive philosophical approach that em-

Box 10: Health and wellbeing logic model in the reinforced palliative home care INTEGRATE-HTA case study (Brereton et al., 2015)

In considering interventions to support carers in palliative care (reinforced palliative home care) this conceptual model identifies how carer support interventions are thought to operate to improve patient outcomes in achieving a good death in their place of choice, to improve carer long term outcomes in coping and bereavement and in reducing the costs associated with avoidable emergency admissions to hospital.

Figure 7: Health and wellbeing logic model for reinforced palliative home care.



plays several components within a structured learning cycle, including:

- the construction of root definitions of the problem situation,
- structured interrogation of the problem,
- development of conceptual activity models and
- rich pictures.

SSM itself is a methodology not a procedure, thus the economic analyst needs to be able to make decisions about how and when to use components of SSM in addressing each problem situation. For example these approaches may be particularly useful in considering a formative economic evaluation, where for example significant conflict between perspectives requires a search for novel interventions or options for change.

Cognitive Mapping is a technique for modelling a person or groups 'thinking' with regard to a problematic situation. It shares similarities with causal mapping and mind mapping but through the use of an explicit format and structure provides for analyses that allow for a clarity that reflects the richness of group perceptions rather than achieving clarity through simplification (Eden & Ackermann, 2004). Cognitive mapping is founded on Kelly's personal construct theory that people continually strive to make sense of the world in order to manage and control it. This sense making involves a setting in order of the facts of human experience. It uses the problem owner's own language to define action oriented concepts and sets these in an ordered causal chain moving from possible actions to goals. This conceptual model thus facilitates the whole system to be modelled and allows analyses to identify the heart of the problem, allows issues to be raised and investigated, allows the boundaries of the system to be explored and goals to be clarified and options to be realised.

Some of the benefits of cognitive mapping techniques are:

- it's a systemic method that deals explicitly with action focused concepts and the relationships between them,
- it's basis in personal construct theory means that it is explicitly designed for capturing stakeholder perspectives and can be used with the individual or group,
- it's focus is explicitly on hypothesised causality 'A may cause B' rather than 'A causes B', this makes it particularly appropriate for dealing with subjectively defined causal relationships, the strength of the evidence for key causal links in the chain can then be the subject of subsequent detailed assessment,

- it comes with a set of analytical techniques for analysing the structure of a problem situation that is well suited for identifying aspects of complexity such as multiple perspectives and causal feedback loops in large and complex systems,
- it provides a structured method with detailed guidance and case studies for training.

These features of cognitive mapping make it a potentially useful method in developing the health and wellbeing logic model, depending on the availability of time and resources for this stage of the economic assessment and the complexity and scale of the problem.

The modeller will need to select the most appropriate method and this choice should be made with regard to project time and resource constraints as part of the 'aligning the process with the decision problem' step (Step2).

Step 3 - Stage 2b: Design oriented conceptual modelling

KEY DELIVERABLE: A written document outlining the design and specification of the economic model and justification of choices made relating to the specification.

This stage is concerned with the specification and design of the quantitative model that will be used to generate estimates of economically relevant outcomes. Once again this stage is primarily one of choice and judgement, involving iteration with the development of the problem oriented conceptual models and further information gathering exercises.

Documentation detailing and justifying design choices should be produced to ensure model credibility with decision makers and stakeholders.

Key deliverable outputs of this stage are:

- Definition of the type of model (for example Markov, decision tree or analytical),
- A visual diagram of the model appropriate to the above type,
- Specification of the functional relationships and parameters forming the model,
- Description of approach to parameterisation (for example calibration, synthesis or both) and
- Specification of data sources.

Taxonomies exist for helping to select the appropriate model type based upon the characteristics of the health economic problem.(Brennan et al., 2006) Squires reviewed these taxonomies and finds that they do not take into account issues of complexity associated principally with heterogeneity of response within the modelled population.

on and communication through social or spatial networks. This guidance, therefore recommends the use of an expanded taxonomy identifying the place of agent based simulation. (Squires, 2014; Siebers et al., 2010) The key aspects of the problem governing the selection of model type relate to aspects of complexity namely, whether interaction, timing, stochasticity and heterogeneity are important, and whether there is sufficient evidence for the different methods to be feasible.

A decision regarding the boundary of the model is needed. The specification of the functional relationships and parameters defines the boundary (ie deciding what factors of the decision problem are included within the model) and depth of the model (ie defining how those factors are represented within the model). The boundary should be such that all factors and interactions between factors that are judged as likely to have an important impact on outcomes are included. It is the transparency and consensus about this judgement that underpins model credibility and validity, it is therefore important to tabulate inclusion and exclusion judgments (Robinson, 2011). These judgements should be made with reference to the aspects of complexity described in the earlier problem structuring stages. It should be noted that this is potentially an iterative process since it is this close consideration of the boundary of the quantitative model that determines when our understanding of the decision problem is sufficient. Thus reflecting on the important elements to capture in the quantitative model may lead us to return to and develop our understanding of the decision problem.

The separation of the problem oriented and design oriented conceptual models allows simplifications and assumptions in the quantitative model to be compared against the conceptual counterpart, thereby facilitating debate and justification (Tappenden et al., 2012).

Furthermore, this separation allows decisions to be taken concerning the level of complexity captured within the quantitative model. Thus there is a central design choice concerning whether to attempt to include complex aspects within the quantitative model or whether to consciously simplify the model and be clear about its applicability and interpretation.

The choices concerning the complexity of the model rely on balancing:

- ▶ the potential impact of complexity on economic outcomes, that is will or when will the complexity matter for decision making,
- ▶ the evidence available to support judgements about the structure and parameterisation of the model,

- ▶ the time, resources and skills available to capture the complex aspects within the model and
- ▶ the purpose and role of the quantitative model in supporting decision making.

Where decisions are taken to exclude complex aspects of the decision problem from inclusion within the quantitative model, these decisions need to be documented to ensure that the outputs of the model are interpreted appropriately. Thus, for example it may only be feasible to generate a very simple model of a complex situation, whilst such a model may not be fit for the purpose of estimating cost effectiveness ratios for a simple commissioning decision, nonetheless it may be sufficient to provide useful information for decision makers. For example in considering:

- ▶ whether there is scope for an intervention to be economically attractive (ie is it feasible that the intervention might be cost saving or cost effectiveness), or
- ▶ what outcomes and levers should be included in the design of an intervention in a system subject to adaptation, to enable the evolution of the system to be managed.
- ▶ what cost and resource evidence should be collected in any subsequent evaluations of a novel intervention.

Thus, when documenting the design and specification of economic models of complex interventions in complex systems it is essential to be explicit about the role and fitness for purpose of the models.

Step 3 - Stages 3 and 4: Model implementation and checking

KEY DELIVERABLE: Delivery of the economic model, with evidence of validation processes undertaken to ensure the robustness and credibility of the model.

Model implementation is concerned with the physical development of the quantitative model according to the design and specification details set down in the design oriented conceptual modelling stage. Methods and techniques for minimising the risks to model credibility associated with this stage of activity are discussed elsewhere (Chilcott et al., 2010). Model checking can lead to iterative development of the design and problem oriented conceptual modelling. Model implementation is essentially a technical activity and is independent of complexity in the underlying decision problem.

Step 3 - Stage 5: Engaging with the decision problems

KEY DELIVERABLE: Presentation of the outputs of the economic modelling in an appropriate manner to facilitate decision making

Three processes are identified in decision making:

1. Definition of decision making criteria
2. Discovery of options and assessment of the evidence regarding impact of options on criteria and
3. Decision making through appraisal and valuation of the evidence on impacts.

Conventional health economics guidance expresses a preference for cost utility analysis / cost effectiveness analysis (CUA/CEA). When considering complex interventions in complex settings where multiple stakeholders are involved with multiple perspectives, there is potentially an important role for cost consequence analysis (CCA). This guidance recommends consideration of the use of a CCA approach to enable the economic model results to be presented and considered from a range of perspectives. The framework does not seek to impose a formal decision making method such as Multi-criteria Decision Analysis (MCDA) onto the decision maker but seeks to support a deliberative decision making process. (That being said the approach is generally compatible with an MCDA approach, if that is appropriate.)

Definition of decision making criteria:- The understanding of the decision problem stage (Step 3 : Stage 1) will have identified the perspective and key outcomes of interest for each of the stakeholders identified in the system that is the subject of the HTA, that is the customers (eg patients), actors (eg healthcare professionals) and problem owners (eg healthcare commissioners). These outcomes constitute the decision making criteria for examination in the CCA. It should be noted here that the importance of CCA in addressing decisions concerning complex interventions in complex systems is not due to the difficulties in obtaining cost effectiveness measures, but rather as a means of satisfying the different decision making needs of the multiple agencies involved in the system.

Discovery of options and assessment of the evidence:- In many cases the definition of the intervention or options of interest may be pre-specified by the client. Where this is not the case the conceptual modelling with the Stakeholder Advisory Group in 'understanding the decision problem' and 'problem oriented conceptual modelling' can be used to generate options for assessment. The economic model will be used to produce estimates of the key outcomes, including a presentation of parametric and structural uncertainty, for the interventions and comparators under assessment.

Limitations of the model in relation to its inability to address any of the identified issues raised by complexity should be clearly acknowledged and the impact of this on the results highlighted to ensure transparency.

The ability to translate the findings between contexts and settings should be explicitly considered and the limits of

their applicability should be clearly presented. A defining characteristic of complex interventions in complex settings is that they are commonly unrepeatable and are very setting or context specific. Reports of economic evaluations should, therefore, give an explicit consideration of translation between settings or setting specific analyses.

Appraisal and valuation:-The key outcomes, including both costs and health and wellbeing outcomes, need to be tabulated for each stakeholder in the system. As a first step in aiding the deliberative decision making process the CCA should identify trade-offs inherent within the outcome sets a) for each stakeholder and b) between stakeholders. The cost consequence analysis can then be used to:

- a. Identify feasible solutions that all parties can live with
- b. Identify potential for transfer payments between stakeholders to enable feasible solutions to be found

If none of the existing options are assessed as feasible, that is are not acceptable to all stakeholder groups, then the problem oriented conceptual modelling can be re-examined in light of the constraints identified in order to search for alternative feasible options, for example adaptations to the intervention design to ensure feasibility.

3.4 CONCLUSIONS

3.4.1 Main insights for the integrated assessment of complex technologies

The review of existing health economic guidance within HTA highlighted that intervening in complex systems raises a number of issues for economic evaluation which are not addressed by current HTA guidance. In particular key characteristics of complexity, including the existence of multiple perspectives and the potential for adaptation and co-evolution are not addressed. In response to this we developed guidance that includes recommendations for methodological research to address the issues raised by complexity and recommendations for practice that focus on the use of a systems approach for undertaking model based economic evaluation of complex interventions in a complex setting. The guidance on practice is based on a combination of problem structuring methods and quantitative modelling. Whilst conceptual frameworks exist for structuring the consideration of public health interventions (NICE, 2009) no similar conceptual frameworks exist for more generic complex interventions.

A systems approach to economic evaluation provides a useful conceptual framework for addressing a number of

the issues by complexity. It takes as its starting point Step 1 of the INTEGRATE-HTA Model in which the HTA objective is defined and preliminary definitions of the technologies of interest are presented, along with the specific logic model generated for the technology of interest as part of Step 2. The problem oriented conceptual modelling for the economic model expands on the thinking within the technology specific logic model by developing descriptions of the health systems that enable the potential impact of the intervention on economically relevant outcomes to be made explicit. Specifically use of a systems approach assists in developing an understanding of the decision problem and scope for economic evaluation, based on an iterative, consultative process. In addition the conceptual modelling stage allows in-depth exploration of the issues around indeterminate phenomena (for instance, better understanding of potential variation around the intervention and how it is delivered, along with variation in the system into which it will be introduced) and uncertain causality (eg the range of factors that may influence how the intervention impacts on the system and the resultant outcomes). The systems approach also facilitates an increased role for cost consequence analysis (CCA) to support decision making in the presence of multiple perspectives. Outputs from the other elements of the HTA - including the effectiveness review, and the socio-cultural and context and implementation elements of the project, can provide a rapid and comprehensive understanding of relevant issues to feed directly into our conceptual modelling exercise. Detailed documentation and discussion of the conceptual models and design orientated models ensures that all stakeholders are provided with a comprehensive understanding of the proposed model prior to implementation to maximise the opportunity for feedback and reflection.

3.4.2 Strengths and limitations of current methods

This guidance does not seek to replace existing guidance for economic evaluation in HTA, but rather to sit alongside such guidance and expand on methods of particular relevance when considering complex interventions acting in a complex health system.

The recommendations for practice can be adopted as part of a systems approach for economic modelling of complex system interventions. The approach seeks to provide a methodology rather than a method, thus there is expected to be significant flexibility in implementation, with design choices necessary in adapting the implementation of the guidance to specific decision making contexts.

It therefore relies on the skills of the economic modeller and requires the use of choice and judgement at a number of stages along the way. It is the transparency and consensus about these judgements that will underpin model credibility and validity. The separation of the problem oriented and design oriented conceptual models allows simplifications and assumptions in the quantitative model to be compared against the conceptual counterpart, thereby allowing for debate and justification. A framework has been provided which should facilitate communication between stakeholders and improve model credibility and validation.

A number of unresolved issues exist for which further research is warranted. Recommendations for research were given in the review. These include methodological development around the potential role of computational complexity science methods to support health economics within HTA, the use of computational modelling techniques, such as agent based modelling and social network analysis for understanding the health economic impact of adaptive behaviour and co-evolutions of intervention and setting within HTA and the modelling of behaviour within health economic models. Furthermore the application of the recommendations for practice aims to be a starting point for further development.

3.4.3 Outlook

The aim of the guidance is to improve the quality of economic models for complex interventions in complex settings. We have sought to provide a systemic approach to understand a decision problem and designing and implementing an economic model in a way that captures the views and perspectives of different stakeholders. This guidance is a starting point for further development. It needs to be validated in different disease areas, with the aim of adapting and improving the current version. Substantial further methodological research is also needed in order to better understand the potential of computational complexity science methods to contribute to health economic modelling in HTA and the impact complexity has on the role of health economics within HTA.

4 GUIDANCE TO ASSESS ETHICAL ASPECTS

By: Kristin Bakke Lysdahl, Louise Brereton, Wija Oortwijn, Kati Mozygemba, Pietro Refolo, Dario Sacchini, Jan Brönneke, Gert Jan van der Wilt, Ansgar Gerhardus, Bjørn M. Hofmann

4.1 INTRODUCTION

4.1.1 Purpose and scope of the guidance

Aim of this guidance

The aim of this guidance is to provide a procedural framework for assessment of ethical aspects of complex health technologies in the context of an HTA. To this end, the guidance should provide:

- ▶ Clarification of aspects of complexity relevant for ethical analyses, on which the complexity of the technology can be assessed
- ▶ Presentation of existing approaches for ethical assessment within HTA, and their applicability for complex technologies, as basis for selection of approaches
- ▶ Guidance on how to adjust existing ethical approaches for handling complex technologies.
- ▶ Guidance on how to take the HTA context into account in the ethical analyses.

How does this guidance relate to other similar guidances in the field?

Many approaches exist for assessing ethical aspects in HTA. A recent review indicates this when they identified “43 conceptual frameworks or practical guidelines, varying in their philosophical approach, structure, and comprehensiveness” (Assasi et al., 2014). This guidance does not seek to suggest new or replace existing approaches for ethical assessment in HTA. Rather it aims at giving advice on

selecting and using existing approaches for the assessment of complex technologies, and procedures for identifying when and how to modify and/or expand existing approaches in order to increase their applicability for complex technologies.

4.1.2 Background

The terms ethical/ethic *approach* or method have been used interchangeably, but in this guidance the overarching term *approach* is used to cover methods and also what would more correctly have been labelled moral theory.⁴ This use of the common concept approach is justified by the common role of all methods/moral theories/philosophical frameworks/tools in this context, i.e. to provide ways to assess ethical aspects of a given technology in the context of a HTA.

Definition of ethical aspects in HTA

Ethics or moral philosophy is the part of philosophy that deals with questions about moral values and norms, i.e., what is good or bad (what is a good life for humans?) and what is right and wrong (what is the right way for a human to act in a given situation?) respectively. In HTA, ethical aspect deals with “moral norms and values relevant for the technology in question”, including prevailing norms and values and the norms and values constructed by putting the technology into use (EUnetHTA, 2015, p. 257). In addition, ethical aspects deal with moral questions related to performing the HTA itself (ibid).

Ethical aspects and socio-cultural aspects of HTA are strongly interrelated,⁵ and therefore often addressed in common in research articles and guidelines (Lehoux & Williams-Jones, 2007; Potter et al., 2008; Braunack-Mayer & Palmer, 2008; SBU, 2014). Hence, collaboration when dealing with these aspects of HTA is advisable.

Problem definition

From the very beginning, ethics has been on the HTA agenda, but general acceptance for incorporating ethics (along with legal and societal aspects) has not gained acceptance until recently (Hofmann,

⁴ It can be argued that the term ethical method have been used too widely to cover approaches/tools that do not fulfil the requirements of a method. The term ethical approach is accordingly more appropriate.

⁵ Ethical and socio-cultural aspects are also strongly interrelated with legal aspect, and are in some contexts labelled ESLI (Ethical, Social, and Legal Issues) research.

2005; Saarni et al., 2008). Assasi et al. (2014) refer to a survey published in a report submitted to the Canadian Agency for Drugs and Technologies in Healthcare,⁶ which showed that only 5 % of the (223) HTA reports published in the period 2003 to 2006 by agencies in Canada, UK, Denmark and USA considered ethical, social and organizational aspects in addition to clinical and economic evaluations. One reason why ethics are rarely incorporated in HTA may be that the feasibility of using the approaches needs to be improved to be feasible to the users. Another reason may be that HTAs assess ever more complex technologies, for which existing approaches for addressing ethical aspects are not suitable. For example, ethical issues may also be more difficult to detect in complex interventions. Complex technologies may also challenge the traditional “add on” approach⁷, highlights the need for investigating how ethics can be integrated in HTA.

On the other hand, it can be argued that the recent focus on the strong implications of complex interventions for systematic reviews and effectiveness assessments in HTA (Petticrew et al., 2013), are less challenging for ethical aspects. Those assessing ethical aspects may be more familiar with including a range of information sources (qualitative and theoretical research, policy documents etc.), and dealing with causes of uncertainty, stakeholder (conflicting) interests etc. Nevertheless, questions about how complexity may influence the assessment of ethical aspect should be addressed, in order to investigate how existing approaches needs to be further adapted.

4.1.3 Complexity and integration perspectives

Characteristics of complex technologies challenging for effectiveness and cost-effectiveness assessment are described in the HTA literature. Two notable publications in the HTA literature (Craig et al., 2008; Petticrew et al., 2013) provide together a list of

twelve complexity characteristics. We investigated how these characteristics can be relevant for ethical analyses and identified 4 overarching characteristics. For instance both the characteristic ‘Number of interacting components’⁸ and ‘Number of groups or organisation levels targeted by the intervention’ are considered relevant because this means that the technology can be viewed from a variety of perspectives, which in turn may raise challenges with conflict of interest, responsibility and justice. As ethical aspects themselves can contribute to the complexity of a technology, we added this into a final synthesised set of five key characteristics: multiple and changing perspectives, indeterminate phenomena, uncertain causality, unpredictable outcomes and ethical complexity. Table 8 provides a short explanation of the five characteristics, and makes use of palliative care (PC) to illustrate the meaning of the characteristics.⁹ Further information of how and why these characteristics are considered relevant for ethical analyses is provided elsewhere (Lysdahl & Hofmann, submitted manuscript).

The understanding of complexity and its relevance for ethical analyses in HTA form the basis for the guidance, the assessment of ethical approaches and the suggested procedural framework. To illustrate the relevance of complexity for ethical analyses in HTA, some implications of the different characteristics are shown in Table 9.

As INTEGRATE-HTA seeks to provide means for integrating aspects when assessing complex technologies, we need to clarify what it means to “integrate ethics in HTA”. Table 10 provides an overview of four different understanding of “integration”, which is also included in the later description of the framework application. For further information on the integration see Hofmann et al. (2015a).

⁶ Original source not available.

⁷ “Add on” approaches means that the ethical analysis is performed in isolation from the HTA process, i.e. an analysis added to, and not incorporated into the HTA (Saarni et al., 2008).

⁸ In health technologies a number of acting people adds to the list of “components”.

⁹ It should be noticed that the illustrating examples have been added into the guidance after its application on home based palliative care. Hence, the use of this example here could not influence the application. It should also be underscored that the examples do not represent the outcome of the application, which can be found in the case study report (Brereton et al., 2016).

Table 8: Synthesis of most relevant characteristics of complexity for addressing moral issues in HTA (Lysdahl & Hofmann, submitted manuscript)¹⁰.

Characteristic	Short explanation, illustrated by palliative care (PC)
1 Multiple and changing perspectives	<p>The variety of perspectives is caused by the many components (social, material, theoretical, and procedural), actors, stakeholders, and organisational levels that are involved in the technology. These are in addition interconnected and interacting, and accordingly exposed to changes.</p> <p>PC includes a number of components due to the holistic perspective (physical, psychological, social and spiritual). It involves multiple actors (various health care providers, organisations, professions, patients, lay cares, families). Interaction between these actors are essential for the services, and unavoidably lead to changes, e.g. in the actors understanding and attitudes towards PC.</p>
2 Indeterminate phenomena	<p>The technologies or condition cannot be strictly defined or delimited due to characteristics like flexibility, tailoring, self-organization, adaptivity and evolution over time.</p> <p>PC is not one single clearly defined/delimited technology; a range of models (also of the more specified home based care) may exist within a single country or geographical region. Likewise there is no a clear cut definition of the condition of the target population, regarding type of disease and when in the disease trajectory it should be provided.</p>
3 Uncertain causality	<p>Factors like synergy between components, feedback loops, moderators and mediators of effect, context, symbolic value of the technology lead to uncertain causal pathways between intervention and outcome.</p> <p>PC aims at being sensitive to the preferences of patients and relatives and is highly adaptive to context. For instance: the relationship between patient and relatives, their interaction with providers may change and consequently change the course of care, and its outcome.</p>
4 Unpredictable outcomes	<p>The outcomes of the technology may be many, variable, new, emerging and unexpected. Because of the holistic perspective of PC, the different target populations (patients with different diseases and their relatives), and differences in individual needs there are a range of outcomes. As the PC services continuously evolve, new and unexpected outcome may appear.</p>
5 Ethical complexity	<p>Some technologies are especially ethically complex because basic ethical principles are contradicting or because fundamental moral or sociocultural values are at stake.</p> <p>There may not be any contradiction between basic ethical principles embedded in PC, but it can be argued that fundamental moral values are potentially at stake. Recipients of PC services are in a very vulnerable situation, where dignity of humans is an essential value.</p> <p>The case of the Liverpool Care Pathway in UK shows that technologies for end-of-life care can cause public controversy.¹¹ Home based palliative care technologies has similar potential for public controversy if the ideal of respecting patients and relative wishes for home death, tends towards being perceived as a pressure, motivated by economic gain.</p>

10 The characteristics included here is identical to the ones in used in the effectiveness (2.1.3) and economic section (3.1.2), except for the fifth one. From the perspective of ethical assessment the broader category 'historicity/path dependence' is considered covered by other characteristics (indeterminate phenomena, uncertain causality and unpredictable outcomes). Instead the fifth characteristics of ethical complexity are included to cover the fact that ethical aspects may themselves contribute to an intervention's complexity.

11 The Liverpool Pathway aimed to "transfer the excellence of hospice-based care of the dying into other health care contexts, including the acute hospital" (Davis & Tomas, 2014). Despite the noble intention it was subject to media scrutiny for the late 2012, where it was considered as "little more than a 'money-making tool' for acute trusts to reduce length of stay figures... [and] inappropriate use of the pathway as a surrogate for clinical responsibility came to the light" (ibid).

12 The indeterminacy of complex interventions allows for interpretations in different, also contradictory, ways, (i.e. paradoxes need careful scrutiny and conciliation of interpretations to be resolved) (Hofmann, 2001).

Table 9: Some implications of synthesised relevant complexity characteristics for ethical analyses in HTA (Lysdahl & Hofmann, submitted manuscript).

Characteristic	Implications for ethical analyses in HTA
1 Multiple and changing perspectives	To address the variety of perspectives (typically the stakeholders' interests and intentions), questions about normative implications of inter-connectedness and interactions between actors/components, and moral questions related to control and decision making.
2 Indeterminate phenomena	To identify moral challenges related to indeterminacy of the technology and/or the target medical condition(s). E.g. identify possible contradictory interpretations ¹² and alternative use of the technology, and the justifications of these.
3 Uncertain causality	To address morally relevant issues related to methodological choices in the HTA itself. The uncertainties call for transparency and justification of the choices and an integrative approach.
4 Unpredictable outcomes	To address ethical challenges with handling outcome uncertainties, regarding outcome type, - size, - for whom/at what level, and at what time.
5 Ethical complexity	To reveal underlying norms and values, to elucidate possible contradicting principles or values (resolvability). To reveal potential fundamental ethical, social, cultural values at stake, and contribute to handling of conflicting concerns. Clarity of aim and scope of ethical analyses (conclusiveness and integration in HTA), and comprehensiveness and transparency of reporting are essential.

Table 10: Meanings of the term integration relevant for ethical analyses in HTA (Hofmann et al., 2015a).

Integration label	Explanation
Subsume	To subsume something as part of something more comprehensive. Accordingly, ethics is a subsidiary activity, a sub-project of an HTA, resulting in a separate (subordinate) chapter in a HTA publication/report. Both the activity and the end result (chapter in report or published article) may be less important in the subsequent decision making process.
Combine	To combine (unite) parts or processes. Assessment of the ethical issues is a separate activity (project) on equal terms with the assessment of efficacy, effectiveness, safety, and efficiency. Ethics is an autonomous part of the HTA in its' own right. Its role in the decision making process is on the same footing as other parts of HTA.
Coordinate	To coordinate parts or processes, e.g., in horizontal or vertical integration. Ethics is still a separate part or process in HTA, but its role and importance may vary depending on the context, e.g., the technology to be assessed, the patient group involved, assessment of efficacy, effectiveness, and safety etc. The role of ethics may be different in the assessment of whole genome sequencing of cell free fetal DNA in pregnant women's blood and the assessment of pulseoxymetry in anaesthesiology. Results from the assessment of safety may influence the ethics assessment, and conversely, ethically controversial issues may direct the safety assessment. Although ethics is a defined and context sensitive part of HTA, it still is autonomous. The content of the various parts of HTA may influence each other, but not the approaches as such. Economists assess efficiency the way they seem to be most suitable, and ethicists define their core concepts and do ethics the way they find the best, independent of the other disciplines.
Interact	Interaction (emergence, synergy): Constitutive interaction between ethics and other disciplines. The ethics assessment influences, is influenced by, re-defines and is re-defined by other parts and elements of HTA. E.g., the selection of end-points is informed by and influenced by ethical concerns or patient perspectives. Economic evaluation may be redefined by ethical considerations of equity and non-discrimination, and ethical considerations may be informed and influenced by challenges with elaborating models in economics. While coordination involves mutual adjustments, interaction encompasses reciprocal re-definition.

Table 11: Presentation of selected ethical approaches.

Short descriptions of frequently used ethical approaches in HTA, extracted from (Hofmann et al., 2015a) ¹⁵	References ¹⁶ to further descriptions	References to examples of applications
Principlism is an approach applying four important, but not absolute (prima facie), principles, i.e., respect for autonomy, beneficence, non-maleficance, and justice. It may be necessary to infringe single principles when the principles conflict.	Beauchamp & Childress, 2001	Gallo, 2004; Strech et al., 2013
Casualstry is an approach in ethics for developing and justifying moral judgments with high affinity to medicine, law, and religion. The key is to find solutions to new and challenging cases based on similar cases where solutions exist.	Reuzel et al., 1999	Hofmann et al., 2006
Wide Reflective Equilibrium (WRE) is a method of moral argumentation that starts with gathering existing judgments about a given case and identifies which moral principles are at stake and that guide the judgments. Then it finds (potential) background theories that support the ethical principles and tries to obtain optimal coherence between judgments, principles, and background theories.	Daniels, 1979; Daniels, 2013; Reuzel et al., 2001	Bauer, 2002; Buchanan et al., 2000; Cotton, 2009; Gibson et al., 2012
Social Shaping of Technology (SST) view technology as the product of societal processes within industry, research institutes, governmental bodies, and society at large, rather than an independent artefact that has a certain, measurable impact on its target. Therefore it is important to understand the engagement and strategies of various actors, and the way various problems are defined and resolved. Assessing the role, merit, and value of technology becomes crucial. If technology in fact is technology-in-context, then both technology and its context can be influenced or adjusted to improve the outcomes of using technology.	Clausen & Yoshinaka, 2004	Institute of Health Economics, 2012; Komduur, 2013
Interactive Health Technology Assessment (iHTA) is a specific type of HTA which seeks the active participation and interaction of stakeholders in the process of evaluating a technology. It aims at agreement on what needs to be researched (relevance), how this can best be done (methodology), and how the results should be interpreted and acted upon (practical reason). As such, iHTA is a specific type of participatory evaluation, with a strong emphasis on social learning. The role of the researcher is to identify stakeholders, engage them in the evaluation process, and reconstruct the interpretative frames that they bring to bear on the technology. The aim is to build a research agenda which is considered relevant, plausible and feasible by all stakeholders and to foster ownership of the evaluation.	Grin et al., 1997; Reuzel et al., 2001	Reuzel, 2004
The triangular model, known as “personalist model”, is rooted on the human person (body-soul unitarity) as reference-value in the reality, according the Aristotelian-Thomistic view. Consequently, the human person is the aim and the source of the society. This approach includes factual, anthropological and ethical data in a “triangular” normative reflection process. The three steps of ethical process are: 1. Data collection (knowledge level); 2. Ethical/ anthropological analysis (justifying level) according the following principles/ operating criteria: a. the defence of human physical life; b. the interconnection between personal freedom and responsibility; c. the therapeutic principle, according to which the human person has to be treated as a totality of body and soul; d. the principles of sociality and subsidiarity, for which public/private bodies are called to help all persons, namely when they are not able to fulfil their needs; 3. ethical assessment or appraisal that should address and facilitate the practical choices.	Sacchini et al., 2009; Sgreccia, 2012	Sacchini et al., 2014
The HTA Core Model is a standardized synthesis of available methods intended to address ethical considerations in the whole HTA process (Lampe et al., 2009a). It emphasizes the value-ladenness of technology and HTA, and intends to be practical, transferable, and to consider ethical issues already in the planning phase of the HTA. A range of ethical issues are identified using a question-based format, adapted from the Socratic approach (Hofmann, 2005). An ethical analysis is based on a reflection on stakeholders’ interests, the purpose of the HTA, the characteristics of the specific technology, and the questions, as well as results from the domains of effectiveness, safety and economy. The result of this analysis may be fed back to experts after stakeholder hearings. Conclusions are reported in a structured format in order to enhance both transparency of the argumentation and international transferability.	ELunetHTA, 2015; Lampe et al., 2009b	Saarni et al., 2011
The Socratic approach sees science and technology as a social activity governed by norms and values of various kinds, and aims at highlighting and addressing the overt and covert norms and values involved in the implementation, use, and assessment of a health technology (Hofmann, 2005; Hofmann, et al., 2014). It sets out with identifying characteristics of the health technology and its assessment, as well as the involved stakeholders. To guide the exposure and analysis of value issues involved with a health technology, seven main questions and 33 explanatory and guiding questions are addressed. Not all of the questions are relevant for all technologies.	Hofmann, 2005; Hofmann et al., 2014	Droste et al., 2011; Hofmann, 2012; Hofmann et al., 2013

¹⁵ Descriptions of all approaches are extracted quotes from the article by Hofmann et al. (2015a), except from Triangular model, which was not included in this article. The article provides more information of the approaches in the text, and even more comprehensive in a supplement. Besides, the article includes additional approaches: Utilitarianism, Deontology, Discourse ethics, Constructive technology assessment, Ethical matrix.

¹⁶ For convenience reasons shorter description (papers etc.) are suggested rather than comprehensive books.

4.1.4 Available ethical approaches

The core of this guidance is a procedural framework¹³ for assessment of ethical aspects of HTA of complex technologies. One of its central part is the appraisal and choice (and modification) of ethical approaches. For this reason, we briefly present some of the many approaches for assessing ethical issues in HTA that are relevant for complex technologies.

The selection is based on those approaches most frequently described and used for addressing ethical issues in HTA (Hofmann et al., 2015b). This is a pragmatic choice, assuming well established approaches are robust and applicable. More thorough descriptions of the different approaches are easily available, e.g. in the HTA Core Model (EUnetHTA, 2015), in the survey by (Saarni et al., 2008) and a recent systematic review (Assasi et al., 2014). Additionally, local agency guidelines may present the existing/well established ethical approaches in more detail, e.g. a recent guide from Haute Autorité de Santé, France (Sambuc & Thebaut, 2013) and a method by Statens Beredning För Medicisk Utvärdering, Sweden (Heintz et al., 2015). Table 11 provides a short description of the various approaches, and refers to specific publications for further reading. In addition, references are given to publications where the approach is applied, to illustrate its used in practice.

4.2 GUIDANCE DEVELOPMENT

For the development of the guidance for ethical analyses in HTA of complex technologies various preparatory investigations were necessary:

- a. To investigate how and why complexity of a technology is relevant for ethical analyses and to establish a set of key characteristics (see Table 8) (Lysdahl & Hofmann, submitted manuscript), which will serve as a basis for assessing the ethical approaches applicability for complex technologies. This work mainly draws on the HTA literature on complex technologies.
- b. To identify existing approaches for ethical analyses and assess their applicability for complex technologies according to the set of key characteristics (Lysdahl et al., submitted manuscript). Existing approaches

for ethical analyses in HTA are identified by EUnetHTA (2015), in surveys (Droste, 2010; Saarni et al., 2008) and a comprehensive systematic review (Assasi et al., 2014). We used publications that provide general descriptions and criticism when characterising and assessing these approaches. Primary literature on approaches was identified partly by snowballing overview publications.

- c. To analyse the appropriateness of approaches for integrating ethics in HTA (Hofmann et al., 2015a). Traditional approaches in bio(medical) ethics, processual approaches, and approaches developed for HTA purposes are assessed against dimensions and modes of integration. As argue in the introduction (chapter 1.4.1) the integration of ethics in HTA is highly (but not exclusively) relevant in complex technologies.

The outcomes of these investigations all feeds into the procedural framework, as explained in the next chapter 4.3. (For further details of these investigations, please see the associated publications as indicated). The development of the guidance can further be ascribed to two additional components:

- d. The outcome of, and feedback from, application of the guidance in the demonstration HTA of home based palliative care. The application and its results are available in the case study report (Brereton et al., 2016). A set of seven specific questions¹⁴ were addressed along the application process, which lead to more comprehensive explanations, clarification of concepts, rearrangement of the order of the information, and additional illustration examples in the guidance.
- e. Feedback from external experts, as well as internal reviewers, was obtained by a questionnaire. The questionnaire addressed general questions to all guidances developed in the INTEGRATE-HTA project, as well as specific question to the ethical part. The feedbacks lead to further adjustments and improvements of the guidance, e.g. regarding the integration issue.

¹³ The term procedural framework is used here to substantiate that the components of the framework are procedural steps, accompanied by tools, to guide the user in the assessment process.

¹⁴ The questions addressed: 1. Are the guidance clear, simple, instructive? 2. Are all parts of the content comprehensible? 3. What resources were used regarding time and persons? 4. What possible challenges were identified with each step of the testing? 5. Were experts needed in any part of the testing, either trained ethicist or experts in the intervention (palliative care)? 6. Are the results of the testing comprehensible? 7. Any suggestions for improvements, related to the issues above or anything else?

4.3 HOW TO APPLY THE GUIDANCE

The procedural framework for ethical analyses in HTA of complex technologies consist of a step-based ethical analyses process (centre column), and two contextual¹⁷ areas (HTA /ethical approach context, and health technology context) (see Figure 8). The contextual elements influence, and are influenced by, the steps in the analyses, illustrated by arrows. In the following paragraphs, we will explain the application of the framework step by step.

4.3.1 Assessing complexity of the technology (step 1)

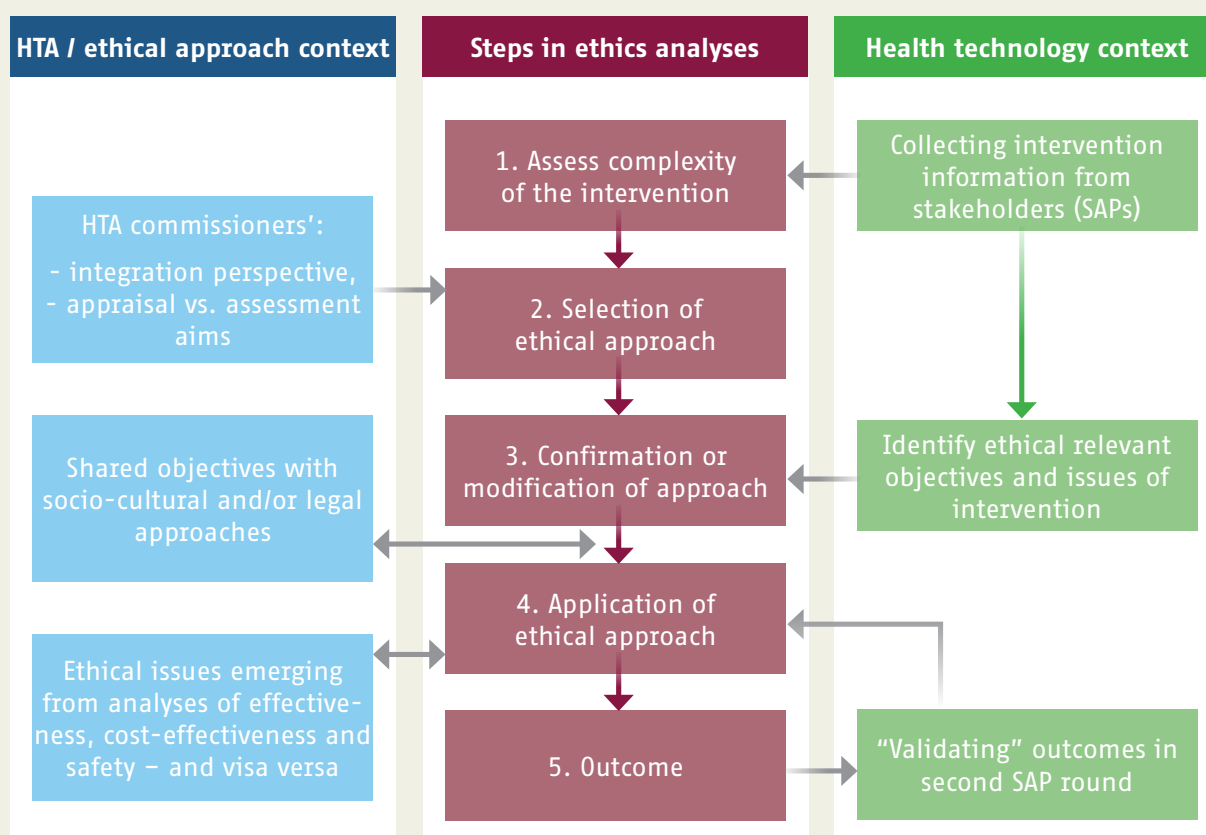
The first step in ethical analyses is to assess complexity of the technology, which will provide the basis for the

subsequent ethical analysis. The five criteria of complexity as described in Table 8 provide a tool for this assessment. This table also gives examples from palliative care technologies in order to illustrate elements that could be included in an assessment.

The main point is not to score the degree of complexity of the technology. Rather, the assessment will provide information about the technologies according to the five criteria, which can guide the selection of appropriate approach(es) (next step). The framework refers to technology in singular. If the task is to compare two or more technologies, please see footnote below.

Sources of information about the technology's complexity can include literature, input from stakeholders, and reflective thoughts' drawing on assessor's existing knowledge. The general advice of involving stakeholders (i.e. patients, relatives, professionals and other parties,

Figure 8: Framework for ethical analyses in HTA of complex technologies.



¹⁷ The term context is defined as follows by (Pfadenhauer et al., 2016): "Context is conceptualized as a set of characteristics and circumstances that consist of active and unique factors that surround the implementation effort. As such it is not a backdrop for implementation but interacts, influences, modifies and facilitates or constrains the intervention and the implementation effort. Context is usually considered in relation to an intervention or object, with which it actively interacts. A boundary between the concepts of context and setting is discernible: setting refers to the physical, specific location in which the intervention is put into practice. Context is much more versatile, embracing not only the setting but also roles, interactions and relationships." This understanding is valid also in this guidance, except that the term focus on the contexts of the HTA process (instead of implementation), in addition to technology / intervention.

researchers, industry), is particularly important in cases of complex technology as the many uncertainties involved entails differences in understanding and attitudes. At the same time it may be challenging to locate and involve all stakeholders due to the large number of different stakeholders/ experts. Stakeholder involvement is emphasized in the framework's technology context column: **Collecting technologies information from stakeholders.** Collecting information from stakeholders should not be a specific task for the ethical assessment, but rather a part of the general information gathering in the initial HTA process. The approaches should be adapted to local expertise and available resources, and could include Stakeholder Advisory Panels (stakeholders as co-researchers) and traditional qualitative interviews of individuals or focus groups. Hence, stakeholder involvement can generate information that is useful in many parts and stages of the HTA, including for assessing the technologies complexity.

Please see the INTEGRATE-HTA Model (Wahlster et al., 2016) for information on an integrated scoping exercise. This model allows for inclusion of different sources of information: from literature, from stakeholder input, and from scoping outcomes from various assessment aspects in the group of INTEGRATE-HTA guidances.

It should be emphasised that this initial step 1 implies a limited level of details in the information collected, or a summary may be needed. The point is to give an over-

view that is easy to use in step 2, when the technology's complexity is to be compared with the ethical approaches applicability for handling complexity.

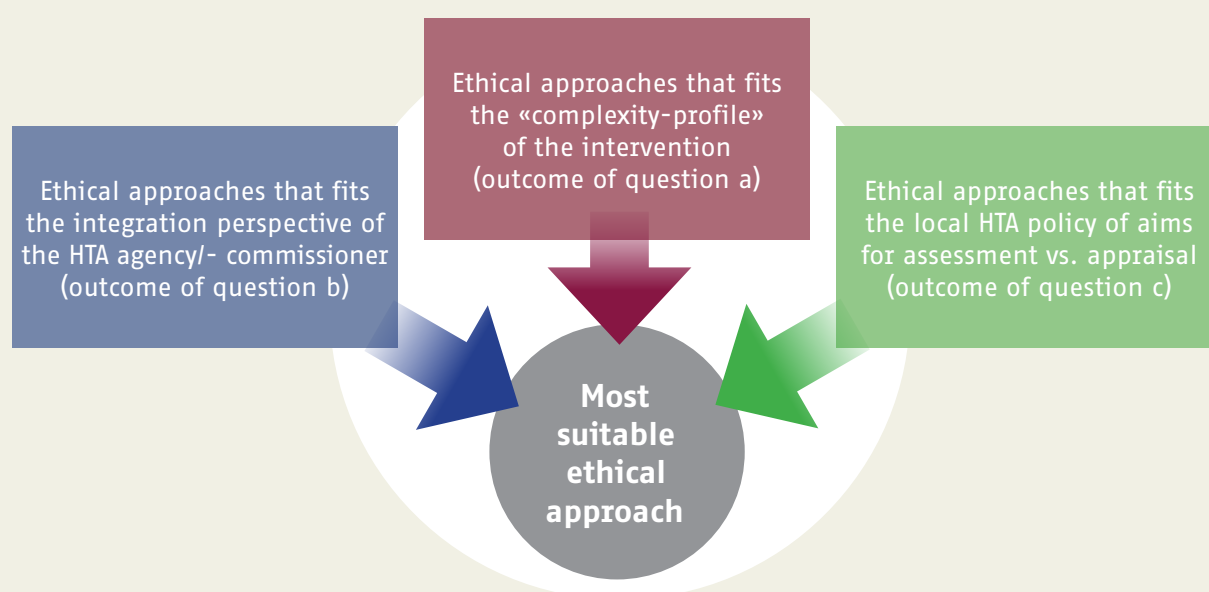
4.3.2 Selecting ethical approach (step 2)

The aim of the second step 2 is to select an ethical approach that best fits the requirements of the complex health technology when applying it in the local context. For this purpose, three questions need to be addressed: how do the ethical approaches fit a) the complexity profile of the technology b) the integration perspective of the HTA agency/- commissioner, and c) the local HTA policy of aims for assessment vs. appraisal (the terms are explained below).

Tools are provided below to assist in answering these questions. For each of the questions the outcome will be a list of ethical approaches that are applicable to a certain extent, i.e. excluding ethical approaches that deemed not or hardly applicable.¹⁹ These three lists are intermediate outcomes in the selection process and have to be considered together in order to identify the overall most suitable approach. The selection process is illustrated in Figure 9.

The tools for selecting an ethical approach should not be expected to give clear cut answers, and the outcomes after addressing the three questions should be ba-

Figure 9: Process for selecting ethical approach.



lanced against one another. To end up with more than one preferred approach is an advantage (rather than a disadvantage, which one may intuitively think) because this give an opportunity to choose an ethical approach appropriate for the context and implementation. This process may be quite challenging for users not familiar with ethical analyses. Hence, consulting an ethicist may be advisable for the second step.

Addressing question a): how do the ethical approaches fit the complexity profile of the technology?

Table 12²⁰ gives an overview of how applicable ethical approaches are with respect to the different aspects of complexity. By comparing this information with the outcome of step 1 it is possible to assess how the ethical approaches fits with aspects of complexity that is deemed important for the technology. The purpose thereof is to identify those approaches that fit (well or fairly well) the important complexity aspects of the technology. For instance, if unpredictability of outcomes is an important characteristic of the technology, the HTA Core Model is a more appropriate choice than Social Shaping of Technology (SST), because the HTA Core Model explicitly addresses the questions of unexpected outcomes, while SST does not focus on outcomes. If on the other hand, indeterminacy of the technology is a prominent characteristic, SST would be a better choice than the HTA Core Model. This is due to the basic understanding in SST that technology and society co-shape each other, which indicates that the approach is well-suited for addressing ethical issues related to this aspect of complexity. Defining the technology and the target group is addressed in the HTA Core Model, but not within the ethical domain. Hence, ethical implications of indeterminacy of technology/condition are not addressed.

Choosing locally developed guides for assessment of ethical aspects

Methodological guides for assessment of ethical aspects developed by local HTA agencies, like the one from The Haute Autorité de Santé (Sambuc & Thebaut, 2013) are feasible to use in complex technology as they should be sensitive to local context. Hence, it is reasonable to add these local guides in to the list of possible approaches and consider the applicability of for complex technologies by applying the same tool used for the more “general” ethical approaches (Table 12). If the local guide

turns out as the overall most suitable ethical approach, question b) and c) below about local context becomes superfluous. However, all subsequent steps in the framework (Figure 8) can be applied for local guides, the same way as for other approaches.

Addressing question b): how do the ethical approaches fit the integration perspective of the HTA agency/- commissioner?

The selection of ethical approach should not be determined without considering the HTA / ethical approach context in which the choice takes place, as shown in the framework’s right context column. The selection should be informed by the **perspective on integration of the HTA commissioner**. This is because different ethical approaches may presuppose certain ways of integrating ethics in the HTA process that may fit more or less to the local perspective on integration. Table 13 provides an overview of the merits of different approaches according to various meanings of integration, subsume, combine, coordinate and interact, are explained in Table 10. Hence, the ethical approaches appropriate for the level of integration in the HTA project can be identified. If the selected approach(es) based on complexity assessment fits poorly with commissioner’s integration perspective, changing the selected approach should be considered. For example, if, based on the complexity assessment, Interactive technology assessment (iHTA) was deemed appropriate, yet the National institute for Health and Care Excellence (NICE) in United Kingdom sees ethical assessment as an activity clearly separated from assessment of effectiveness and cost-effectiveness, one should reconsider this choice. The iHTA approach is not applicable to a subsume/combined understanding of integration, and thus not consistent with the integration perspective promoted by NICE.

Addressing question c): how do the ethical approaches fit the local HTA policy of aims for assessment vs. appraisal?

Finally, one should consider if the selected approach(es) fits the local HTA context policy of aiming for either an **assessment or an appraisal** (as indicated in the HTA / ethical approach context column in the framework). Assessment can be defined as “the action of evaluating relevant aspects of the technology to form a basis for decision, while appraisal implies some form of recommen-

19 The categorizations used in the tools are adjusted to the issues, and hence slightly different: in Table 12: hardly applicable, fairly applicable, and applicable, in Table 13: not applicable, somewhat applicable, applicable, and highly applicable, in Table 14: not/hardly applicable, fairly applicable, and applicable.

20 This assessment in Table 12 is based on the implications of the 5 characteristics of complexity, as described in Table 9, which illustrates some requirements complex interventions pose upon the approaches.

dation about the implementation of the technology, based on this assessment” (Sandman & Heintz, 2014). Due to the prescriptive nature of ethical considerations, the distinction between the two is not a clear cut issue. Still some HTA-agencies are restricted to making assessments, while others may be consulted for recommendations. The advantage of separating the assessment and appraisal tasks is to ensure that political interests do not influence the evaluation. On the other hand, it may be more helpful to decisions-makers to receive an analysis where the merits and strength of the arguments are assessed and balanced against each other (which requires some ethical expertise), i.e. an analysis “closer to” the appraisal (ibid). An overview of how the ethical approaches fit the aims of assessment versus appraisal is given in Table 14. An axiological approach will for instance be more applicable than casuistry to Swedish policy. This is due to the strict separation between The Swedish Council for Health Technology Assessment (SBU), which is responsible for the assessment of the technology, and the county councils, which are responsible for appraising and deciding about implementation (Sandman & Heintz, 2014).²¹

In the tables below (Table 12, Table 13 and Table 14), color-codes (white, grey and shades of blue) are applied to increase the readability. However, the descriptions are the main thing to consider when performing the assessment.

4.3.3 *Confirming and modifying ethical approach (step 3)*

The outcome of step 2 may be a selected ethical approach that does not perfectly fit the important complexity aspect of the technology, as integration perspective and other consideration also have to be taken into account. For this reason a final step, step 3, is needed. This step is to identify possible shortcoming of the chosen approach when applying it to the complex technology in question. Identified shortcomings may make it desirable or necessary to make amendments or additions to the chosen ethical approach. Not taking such actions may distort the assessment and interpretation of the outcome of the ethical analysis. Even in cases where the ethical approach fits the requirement related to complex technologies well, one should always explore potential improvements when applying them.

Information regarding shortcomings and related amendment or additions may arise from general features of the ethical approach and from information on important ethical aspects of the specific technology. Important features of the ethical approaches in general to be aware of and consider in this assessment are provided in Table 15. The outcome of the stakeholder information is a good source for the assessment of whether the selected approach is likely to address important ethical issues of the technology at hand, and consequently, which amendments or additions that may be necessary. Hence, **ethical relevant objectives and issues of the technology** should be identified, and extracted from the qualified stakeholders input/information (as indicated in the technology context column of the framework, see Figure 8. For instance, if Principlism is chosen as a basis approach, we know that there (generally) may be a risk of missing important ethical issues, due to the somewhat narrow scope of only addressing issues related to respect for autonomy, nonmaleficence, beneficence and justice. Hence, one should look out for supplemental ethical perspectives/issues (in the stakeholder information) that may be important when assessing the specific technology, e.g. issues related to dignity, solidarity, responsibility can be important in palliative care technologies.

Finally, the step 2 of the INTEGRATE-HTA process model should be taken into account. The logic model (Rohwer et al., 2016) aims at describing the health technology and the system in which it exists, where ethics is one of the context aspects. The specific logic model contains some key ethical issues, which need to be supplemented with other issues from the scoping process. Additionally, one should address whether the chosen ethical approach is suitable to address identified patient preferences, moderators of treatment effect (van Hoorn et al., 2016), and context and implementation issues (Pfadenhauer et al., 2016). These elements may feed into the analyses and influence the results of the ethical analyses.

The case study of (reinforced) home based palliative care ((r)HBPC) can illustrate how patient preferences and moderators can influence the ethics analysis. The case study revealed that death at home was identified as both a moderator and a patient preference (Brereton et al., 2016). Death at home is a moderator when patients without a caregiver available, or with symptoms that cannot be controlled, as it makes patients less likely to die at home. Death at home is a preference when patients prefer not to die at home because they wish to reduce the burden for

²¹ Other HTA context issues than assessment versus appraisal, such as health policy and institutional/organizational positions may also influence the choice at this point. This may vary greatly between HTA agencies, and is therefore not elaborated on here.

Table 12: Summary of ethical approaches to HTA according to aspects of complexity.

White fields indicate hardly applicable, pale blue fairly applicable and grey applicable (Lysdahl et al, submitted manuscript).

Ethical approach		
	Multiple and changing perspectives	Indeterminate phenomena
Principlism	Limited number of perspectives are included, implication of interactions between agents are partially included.	Questions related to indeterminacy are not addressed.
Casuistry	Analogues can provide solutions taking different perspectives into account, but may not be suitable for joining/synthesizing/compromising perspectives, or to address interconnectedness/interactions.	Analogues can provide potential conceptions of indefinite phenomena, but there is a threat of over-simplification.
Wide reflective equilibrium, (coherence analysis) (WRE)	WRE can take into account multiple perspectives and differences in judgement of moral properties. Interaction between components may be addressed in the WRE process. Control and decision-making is issued by the aim of providing a coherent base for this.	The moral implication of indeterminacy of the technology or condition can be revealed and explored in discussions towards equilibrium.
Social Shaping of Technology	SST aims at taking into account the perspectives of various actors involved in the development and use of a technology. Interactions between technology and society are the main issue.	A level of indeterminacy of the health technology is a fundamental understanding in SST, which paves the way for addressing ethical challenges related to these uncertainties.
Interactive, participatory HTA approaches	iHTA is pre-eminently suited to take into account a variety of perspectives, and interaction between actors.	Indeterminacy of a technology and its use is acknowledged.
The triangular model	A top-down (ethicist based) approach, different perspectives can in the data collection step.	Alternative interpretation of the technology / condition can be thematised when considering available data in the ethical analyses.
The HTA Core Model	Different perspectives are included through stakeholder involvements and cooperation with experts in other HTA-areas. Interactions / interrelations are not specified or related to ethical implications.	Defining the technology and target group is addressed in another domain of the model. Ethical implications of indeterminacy of technology / condition, are not addressed, but an illustration of ethical relevance of defining the target group is given.
The Socratic approach	Identifies actors and stakeholders, and their perspectives, interest etc. Normative implications of interactions between agents (and components in general) are partly covered. Decision-making and responsibilities are also touched upon.	Provides means for exploring various definitions / understanding of the technologies. Moral impact of indeterminacy is not directly addressed, but may be illuminated through related questions.
Ethical guidance developed by local HTA-agency	Fill in	Fill in

Aspects of complexity

Uncertain causality	Unpredictable outcomes	Ethical complexity
Data required by the approach, indicates that methodological choices in the HTA process may be partially addressed.	Ethical issues of outcomes are addressed, but not the uncertainties in outcomes as such.	Resolvability of conflicting principles can be illuminated, but not always overcome.
Analogues may address uncertainties. However, whether the analogues will handle relevant potential uncertainties cannot be predicted.	Analogues may address unpredictability, but it may also cloak basic or dynamic challenges, such as unpredictable outcomes.	Casuistry is excellent for finding solutions to morally challenging problems. However, casuistry does not provide solutions to genuine paradoxes and aporias. It may be useful to highlight them, though.
Do not address moral issues related to methodological choices in HTA in general, but recognise the uncertainties from context dependency and the importance of taking this in to account.	Can accommodate different views of what constitute relevant end points. Unexpected outcomes may be interpreted as disruption of the equilibrium, calling for a renewed debate.	WRE can reveal fundamental values at stake, take value conflicts into account, elucidate contradictions and inform about their resolvability. The aim of WRE is clear, but quality of reporting is not explicitly addressed.
Moral challenges related to HTA methods can be addressed due to the interactive nature of SST.	The approach is by principal not focused on outcomes, but can contribute in identification of unpredictable outcomes.	Fundamental values at stake should be revealed, and the resolvability of possible contradicting principles/values may be elucidated.
Stakeholder involvement in the assessment process facilitates addressing ethical challenges in methodological choices.	The approach is likely to increase the range of outcomes taken into account, which indicate that ethical challenges of this unpredictability are also addressed.	Stakeholders may reveal fundamental moral or socio-cultural values involved, and may elucidate the resolvability of possible contradicting principles/values.
Do not address uncertainty in causal pathway directly, and methodological challenges thereof with moral implications. Takes into account the social context of the human person.	Unpredictability of outcomes is not addressed directly, but may be issued as part of the ethical analyses (i.e. the therapeutic principle).	The approach tries to verify the solvability of conflicting values in the light of personalist framework, clarifies aim and scope of the ethical analyses and contributes to comprehensiveness and transparency of reporting.
Morally relevant issues related to methodological choices are addressed in the introduction, and to some extent in the ethics domain. Factors contributing to uncertain causality is not specifically included, but context are indirectly through context dependent values.	Outcome uncertainties are addressed in the "Beneficence/ nonmaleficence" issue, and in some other part of the model.	Some fundamental values are directly addresses, others may be revealed by stakeholder involvement, which also may reveal contradicting principles/ values. Whereas the contribution to handling conflicting concerns is limited. The (common) reporting structure contributes to transparency.
Morally relevant methodological choices in HTA are well addressed, which can contribute to improvement in taking causal pathway uncertainties into account.	Variety in outcome not specifically addressed, but a series of moral question about different potential outcomes are included.	Reveals fundamental values, and contribute to elucidate contradictions. The clear descriptive aim limits the contribution to handling conflicting concern and contradictions. Comprehensive-ness and transparency in reporting is emphasised.
Fill in	Fill in	Fill in

Table 13: Assessment of merits of various ethics approaches according to various meanings of integration.

White fields indicate not applicable, pale blue indicates somewhat applicable, grey indicates applicable and blue indicates highly applicable (Hofmann et al., 2015).

	Subsume/Combine	Coordinate	Interactive
Principlism	Ethical assessments adopting Principlism are generally performed in a top-down manner (a priori principles where ethical assessments result in a separate chapter in the HTA report and is limited to identifying ethical issues)	The principles are fixed and may be difficult to coordinate with other issues	Ethics assessment has been co-ordinated with other parts of the HTA process, and has played a significant role in the HTA process as well as the forming of the report and its conclusions
Casuistry	Casuistry can be used subsumed or combined, as it may be organized alongside other inquiries of effectiveness, safety, and cost-effectiveness	Casuistry can be used in a coordinated way, adjusted to and adjusting to the other parts of the HTA process	Casuistry is a conservative method, in that it bases the handling new cases on solved solutions. Hence, the background values and principles may not be challenged
Wide Reflective Equilibrium (WRE)	Reflected equilibrium is not obtained in isolation	Equilibrium can result from coordinated parts	As the reflective process can also alter principles, values, and background theories, WRE could be used interactively
Social Shaping of Technology (SST)	Based on social involvement, which is challenging in a subsumed/ combined mode	SST can be used for coordination, but it will not be the most efficient way to apply it	SST is interactive by nature
Interactive technology assessment (iTA)	Based on social involvement, which is challenging in a subsumed/ combined mode	Coordination is ok for iTA	iTA is interactive by nature
The triangular model	Ethical analyses adopting triangular model generally result in a separate chapter in the HTA report. They identify ethical issues and provide moral judgments in a separate and top-down manner	The principles are fixed and hierarchical and may be difficult to coordinate with other issues	As the principles are fixed and hierarchical, it may be difficult to apply in an interactive manner
Axiological (Socratic, the HTA Core Model)	Ethical issues can be addressed independent of and isolated from the other parts of the HTA process, usually resulting in a separate chapter in the HTA report	Ethics assessment has been co-ordinated with other parts of the HTA process, and has played a significant role in the HTA process as well as the forming of the report and its conclusions	Presently being implemented this way, results are uncertain due to limited stakeholder involvement

Table 14: Applicability of ethics approaches according to assessment versus appraisal aims.

White fields indicate not/hardly applicable, grey fairly applicable and blue field indicates most applicable aims.

	Assessment	Appraisal
Principlism	Highlights a range of ethical issues.	Aims at resolving moral conflicts
Casualism	Will normally direct towards specific solutions, and may be less suitable for Assessment.	Aims at resolving moral conflicts
Wide Reflective Equilibrium (WRE)	Will normally direct towards specific solutions, and may be less suitable for Assessment.	Aims at resolving moral conflicts
Social Shaping of Technology (SST)	Aims at framing and forming technology in accordance with ethical values. May be less suitable for assessment in the traditional sense.	Aims at resolving moral conflicts
Interactive technology assessment (ITA)	May be less suitable for assessment in the traditional sense (limited to highlighting normative issues).	Aims at developing consensus
The triangular model	Highlights ethical issues related to human dignity and human rights	Aims at decision making based on the primacy of dignity of human person
Axiological (Socratic, the HTA Core Model)	Aims at exploring ethical issues	Does not direct the decision making process.

informal carers. This information on patient preferences and moderation (i.e., death at home) would enrich the ethical analysis concerning the conception of vulnerability.

The context is an important input for the ethical analysis. One example is the socio-economic status of recipients which influenced the delivery of care in (r)HBPC, as the professionals highlighted the difficulties created by social deprivation (Brereton et al., 2016). Again, the ethical approach should address the question whether the technology demands more of the recipients than those particularly vulnerable can fulfill, and thereby challenge the norm of equal access to health services.

Implementation issues are important for the ethics analysis. E.g., one issue that emerged from the application of the CICI framework was insufficient funding. Patients did not get what they were promised, and felt they were not being worth the investment (of e.g. a wheelchair) (Brereton et al., 2016). In the case study this adds to the identified ethical issue of trust by explicitly pointing to the value of truth telling and dignity in this specific technology.

In summary, patient preferences, moderators, context and implementation issues can be important input for the ethical analyses, and should be taken into account for the purpose of modifying and applying the ethical approach. On the other hand, the outcome of ethical analyses can also provide valuable information for application of the logic model and the CICI framework, supporting the added value of integration.

4.3.4 Applying the ethical approach (step 4)

It is beyond the scope of this guidance to describe in detail how to apply each of the ethical approach that may be selected. Instead a short introduction to the different approaches is provided in chapter 4.1.4 with reference to further reading, including examples of applications. The chosen approach may contain elements that seem to overlap with elements in the

Table 15: Features of ethical approaches in HTA to consider for amending or supplementing purposes in cases of complex technologies.

Ethical approach	Features to consider in cases of complex technologies for amendment or supplementing purposes
Principlism	Improvement of the stakeholder involvement process, in order to broaden the scope of ethical analyses.
Casuistry	By using it in an interactive way, some of the shortcomings in addressing uncertainty, unpredictable outcomes, and ethical complexity may be overcome.
Wide reflective equilibrium, (coherence analysis)	Possible improvements in ensuring that minority groups are considered. Improving the decision making when principles are conflicting.
Social Shaping of Technology	Improving how to handle unplanned/unintended use of the technology. Acknowledge organisation and institutional limits of the approach.
Interactive, participatory HTA approaches	Possible improvements in ensuring representative participation of all involved parties
Triangular model	Improvement of the stakeholder involvement process, in order to broaden the scope of ethical analyses.
The HTA Core Model	Improvement possible by addressing the many complexity aspect in a more systematic way, and clarification of the link between the methodological approaches and assessment tables.
The Socratic approach	Improvements possible by addressing questions of decision making and responsibility, and the moral impact of indeterminacy and uncertain of outcome.

framework presented here, e.g. involving stakeholders is crucial point in many of the approaches. One should consider the need for supplementing the information already gained, e.g. if the purpose of stakeholder involvement differs between the framework and the chosen ethical approach. Literature review is a relevant method for many of the ethical approaches. Guidance on how to perform literature review on ethical issues is provided in articles by Droste et al. (2010) and Strech & Sofaer (2012), and in the chapter 'Ethical analyses' (Lysdahl & Droste, 2015) in the HTAi vortal: Summarized Research in Information Retrieval for HTA (SuRe Info).

It may be advisable to consult an expert if the assessor is not an ethicist, or not familiar with the chosen approach. The need for such consultations may vary depending on the chosen approach, e.g. be less for those developed specifically for HTA (the axiological) and those regarded simple to use (Principlism).

Before applying the selected ethical approach the whole HTA process may profit from exploring possible **shared objectives with socio-cultural and/or legal approaches** (as indicated in the HTA / ethical approach context column in the framework). One reason for this is the potential overlaps between the methods for assessing the ethical, socio-cultural and legal aspects of HTA. Examples of common issues that can be identified in the case of palliative care technologies are: access and availability, patient/professional relationship and shared decision making. Responsibility and autonomy are typically common issues for all three.

A joint assessment of common issues entails a risk of losing information, because the issues may be understood and assessed differently from the different perspectives. Nevertheless, it may be labour-saving to investigate these issues (partly) in common and/or (if different assessors are involved) to collaborate about the investigation(s), e.g. about literature review when this is a relevant rese-

arch method. Besides this rather pragmatic reason, the outcome of the HTA may be enriched by assessing these issues in an integrative manner. By including different perspectives (ethical, socio-cultural, legal) when investigating same/similar issues may increase validity and add value to the HTA.

In addition a complex technology requires some level of integration of other aspects in the HTA. For the application of the ethical approach it is important that **ethical issues emerging from analyses of effectiveness, cost-effectiveness and safety** are addressed in the ethical analyses. For instance can the cost-effectiveness analysis point out a need for addressing questions about prioritization and fair distribution of resources, or the safety analysis may point to a need for analysing the distribution of risk between stakeholders. As indicated in the HTA / ethical approach context column in the framework: there is a bilateral need for integration between aspects of the HTA process. There is a need for ethical aspects to inform the analyses of other aspects of the HTA. The classic example is the importance of making sure that the decisions about outcome measure corresponds with stakeholders' perception of outcomes that matters to them, i.e. what they considered valuable. In case of the cochlear implant, the research was originally focused on outcomes on hearing and the understanding and production of spoken language, while a major concern of Deaf Communities was the survival of Deaf Culture, was not well reflected in the assessed outcomes.

4.3.5 Outcome of ethical assessment (step 5)

The outcome of the ethical assessment should be validated by the different relevant stakeholders. The aim is to find out if the outcome makes sense to them, if important ethical issues are included and handled in a sensible way. Again an integrated approach should be considered, i.e. to involve stakeholders in assessing the outcome of the HTA in general (not separately for ethical aspects).

If deficits of the analysis outcome are revealed in this process, e.g. due to lack of data or scarce information on a new technology, supplemental analysis should be performed. This iterative element in the ethical framework is important because of the many uncertainties in complex health technology.

4.4 CONCLUSIONS

4.4.1 Main insights for the assessment of complex technologies

Complex technologies pose high demands on the approaches and skills in assessing ethical aspects of HTA. Existing approaches in ethics vary in their ability to meet such demands. This document makes the user aware of these differences, and provides guidance on how to assess the complexity of a technology, to choose between ethical approaches, and to make relevant amendments in order to assess specific complex technologies in their own HTA context.

4.4.2 Strengths and limitations of current approach(s)

Complex technologies are context dependent, and may raise a wide range of ethical issues. Hence, they do not allow for one-size-fits-all approaches. Therefore, the flexibility of the procedural framework for assessment of ethical aspect in this guidance may be appropriate for complex health technologies.

The alternative strategy, to select one specific approach or to design an ethical approach specifically for complex technologies, does not seem feasible as complex inventions do not lend itself to a simple unified typology. Hence, although a simple single approach would be preferable, the subject matter does not allow this, and it appears that we have to accept a complex approach.

However, the flexibility may be demanding and presuppose some ethical expertise or consultation by ethicist, e.g. for choosing and amending the ethical approach.

4.4.3 Outlook

This guidance contributes to the understanding of complex health technologies and the implication for ethical assessment in HTA. The procedural framework presented is designed to guide the ethical assessment of complex health technologies. However, the value of this framework depends on its usefulness as experienced when implemented by HTA agencies. Future research should therefore focus on questions around the applicability of the procedural framework for ethical analyses on various complex health technologies, in various settings.

5 GUIDANCE TO ASSESS SOCIO-CULTURAL ASPECTS

By: Kati Mogyemba, Bjørn M. Hofmann, Kristin Bakke Lysdahl, Lisa Pfadenhauer, Gert Jan van der Wilt, Ansgar Gerhardus

5.1 INTRODUCTION

5.1.1 Purpose and scope of the guidance

Aim of this guidance

This guidance aims to provide a five-step-process to assess socio-cultural aspects in Health Technology Assessment (HTA) (see Figure 11). It also provides a socio-cultural framework (see Figure 10) that can be applied to steps 2 to 5 of the assessment process. The guidance can be applied

- ▶ to identify and prioritize important socio-cultural aspects/ discourses as well as heterogeneous perspectives related to a health technology,
- ▶ to identify and involve various stakeholders and stakeholder groups,
- ▶ to determine research agendas on socio-cultural aspects, and
- ▶ to assess socio-cultural aspects linked to a certain technology in a culturally sensitive way.

The added value of this guidance in relation to existing guidances

Although socio-cultural aspects are rarely considered in HTA (Arellano et al., 2009; Draborg et al., 2005; EUnetHTA, 2015; Lehoux et al., 2004), some methodological guidance exist. Searching the websites of the 56 INAHTA-member agencies up to September 2013, we identified ten agencies which either present their own considerations to address social aspects in HTA (e.g. Kristensen & Sigmund, 2007) or refer to the HTA Core Model (EUnetHTA, 2015) or the Model for Assessment of Telemedicine Applications (MAST) (Medcom & Norwegian Centre for Integrated Care and Telemedicine, 2010). The information on methodological approaches and the understanding of socio-cultural aspects presented in these documents informed our guidance. Combined with the information gathered from empirical studies on socio-cultural aspects of health technologies, we were able to inductively and systematically

develop a framework for the assessment of socio-cultural aspects taking empirical studies from different fields and HTA-practice into account (see 5.2).

Compared to other guidances, this guidance offers approaches which frame a) the HTA as a whole (e.g. Social Shaping of Technology, Constructive Technology Assessment) and/or b) which frame the understanding of specific aspects such as "social inequality". Additionally, the guidance offers a tool for the identification and assessment of different cultural perspectives.

The guidance also adds the reflection of stakeholder involvement in HTA and offers concrete methods that can be applied in all relevant assessment steps (see 5.3). Furthermore, the guidance systematically takes the complexity of a health technology into account.

5.1.2 Background

Importance of addressing socio-cultural aspects in HTA

There is no dispute regarding the importance of socio-cultural aspects in health and health care. For example, the World Health Organization (WHO) focusses on social determinants such as social inequality, stigmatization, social isolation, social support etc. and shows their strong influence on good or poor health (e.g. Marmot & Wilkinson, 1999). However, socio-cultural aspects play a minor role in HTA, although they strongly influence how health technologies are used, accepted and assessed by patients and their networks, and by professional providers and decision makers. Different groups will also address and value socio-cultural aspects differently, which could influence the provision of a health technology (e.g., through professional cultures or team structures) as well as its success or failure. For instance, the institutionalization of palliative care in an inpatient hospice can fail in a community characterized by a culture of strong family support.

HTA as established by the US Congress in 1975, focused on the "social impacts" of medical technologies as well as on "questions that might be asked" in such an assessment (Office of Technology Assessment (OTA), 1976, p.3). The Office of Technology Assessment defines "social implications" of a technology as "... direct or indirect effects of medical technology on concepts, relationships, and institutions society considers important" (Office of Technology Assessment (OTA), 1982, p.12). Thus the lower acceptance of the definition of brain death (a socio-culturally shaped concept) for ex-

ample led to a slowed down implementation of organ transplantation in Sweden (Banta, 1993). At the same time the implementation of transplantation technology is likely to change the socio-cultural concept of organ transplantation. Telemonitoring can be taken as an example of a technology's influence on social relationships. It allows for quick intervention in emergencies and reduces the number of visits to the general practitioner. At the same time, telemonitoring is linked to a higher degree of (social) control, and an emphasis of technical data, which increase the degree of distance in the user-professional-relationship (Gerhardus & Stich, 2014).

Socio-cultural knowledge sets the conditions for the technology's viability, the idea of its benefit and the way decisions are made. Knowledge about the socio-cultural aspects of a technology helps the identification and understanding of mutual interactions between society and technology. An example is the implementation of health technologies such as the da Vinci surgical robot despite the high costs involved and a lack of evidence showing its benefits (Abrishami et al., 2015). Instead, the achievement of clinical and scientific excellence, and entrepreneurship advantages supported the implementation: "Surgeons and hospitals wanted to pioneer the provision of this high-tech, high precision surgical platform as a symbol of good care, while also conducting research and performing better than the competitor" (ibid, p. 369).

Socio-cultural aspects can be relevant as (pre-)conditions for the use of a health technology, as part of the intervention itself, as an outcome measure, or as a characteristic of the target group. Implementing and providing a health technology also mutually interacts with the socio-cultural context. The understanding of the concept of socio-cultural aspects is thus of importance since it will define and limit the scope of research questions and form the basis for methodological decisions.

Sensitivity on cultural differences and an understanding of different perspectives of stakeholders valuing a technology could also turn HTA into a social learning process (e.g. Rip et al., 1995; Schwarz & Thompson, 1990; Wynne, 1995). This also includes decision making processes. The emphasis is then on the communication process including scientists, decision-makers and advocates, and not primarily on the document (the HTA-report) (Farrell et al., 2001). Understanding assessment and decision making as social processes "directs attention beyond the content of assessment

reports to encompass questions regarding participation, context, presentation, evaluation and the negotiation and legitimization of boundaries between scientific and policy dimensions" (Farrell et al., 2001, p.312).

Already in 1982, the Office of Technology Assessment (OTA) stated that more investigations concerning social aspects in technology assessment were needed (Office of Technology Assessment, 1982). A statement which, although a limited set of approaches is available, still applies today.

Definition of social, cultural, and socio-cultural aspects in HTA

What is meant by social or cultural aspects is rarely explicitly defined. Neither the INAHTA HTA glossary (INAHTA et al.), the EUnetHTA Adaptation Glossary (beta) (EUnetHTA) nor the Cochrane Collaboration Glossary (Cochrane Collaboration) offer a definition for social, cultural or socio-cultural aspects. In the following we present our understanding of social, cultural and socio-cultural aspects, and describe how these terms are used throughout the guidance.

Social aspects refer to a wide range of topics and issues that are related to the interpersonal organization of human cohabitation. They are represented in social norms, i.e. in shared patterns of thoughts and behaviour and ways social relationships are organized in a society, community or group. Social norms include shared expectations (represented e.g. in social institutions and role pictures). Individuals incorporate, adhere to, communicate, and influence these norms and develop a social identity during socialization processes. Social control reinforces social norms and regulates deviance on different levels of social organization. For example legal norms (which are specific social norms) can in regulated cases be enforced by imprisonment. Social aspects also comprise the social status of an individual or group in the societal field, which determine social inequalities (i.e. differences in the distribution of resources and potential participation). The sociological analysis divides different levels of social organization which interact with each other: "A macrosocial environment is characterized by societal features such as class structure, labour market, income distribution, and social integration. A microsocial environment relates to settings of everyday life, including family and neighbourhood, social networks, schools, and workplaces" (Kirch, 2008, p. 1311).

We refer to social aspects of health technologies if one or more of the stated aspects of social organization are addressed, without emphasis on cultural aspects as defined in the following.

Cultural aspects: "Culture represents human behaviour as an integration pattern that includes thoughts, communications, actions, customs, beliefs, values and institutions of a race, ethnic, religious or social group. Culture denotes a way of life for an entire society. As such, it includes codes of manners, dress, language, religion, rituals, norms of behaviour such as morality and law, and system of belief. Culture influences behaviour through customs such as use of or abstention from meat, alcohol, and tobacco; the practice of rituals such as circumcision; marital customs such as the prevailing age at which women marry; attitudes toward family size, childbearing, and child rearing; personal hygiene; disposal of the dead; and much else. People's values may be the most significant component of culture that affects behaviour and through behaviour, health" (Williams et al., 2003, p. 189). As such social groups differ culturally, i.e. in the way they "make sense of their world" (Barker, 2004, p. 44f.). Different symbolic meanings and the interpersonal patterns of their interpretation influence a social group's perceptions, thoughts, behaviour etc., which defines membership (Barmeyer, 2010). "Cultural belief systems reflect our values and perspectives and at the same time can close our minds to accepting other ways of thinking and doing" (Kirch, 2008, p. 188f.).

We refer to cultural aspects of health technologies if the emphasis is on norms, values, and symbolic meanings (as defined above).

Social and cultural aspects are closely related to each other. Most definitions also overlap in certain aspects. We refer to socio-cultural aspects if we focus on social and cultural aspects and their mutual interactions. The term "socio-cultural aspects" involves all aspects described for social and cultural aspects described above. We summarize this as follows: Socio-cultural aspects of a health technology, a disease, or a health care system comprise knowledge, beliefs, symbols, conceptions, rules (such as morals), regulations (such as laws), customs, goals (values) institutions and any other capabilities and habits acquired by a group which is specifically related to the health technology, disease, or health care system. It also includes explicit and implicit behaviour patterns, including their embodiment in symbols and artefacts. The essential core of culture consists of historically derived and selected ideas and values that are shared among members

of a group (Sabatier, 2007). The purpose, shape, development, and implementation process of a health technology involves socio-cultural norms and values on different levels of social organization (macro-, meso-, and micro level and their interrelations), and vice versa (e.g. Schwarz & Thompson, 1990). Different socio-cultural groups might understand, assess or be affected by a technology in different ways (e.g. Gerhardus & Stich, 2008).

Problem definition

Although the addressing of social aspects is part of most definitions of HTA, this is rarely done in practice (Arellano et al., 2009; Draborg et al., 2005; Lehoux et al., 2004). Where they are addressed, this is often done in an unstructured and unsystematic way (Lee et al., 2009). This is also true for cultural aspects, which are usually not an explicit part of HTA-definitions. Why socio-cultural aspects are not systematically taken into account in HTA can be traced back to two reasons: a) the lack of clarity of the concept of social and cultural aspects, and b) the lack of well-developed methods for the assessment thereof. The lack of clarity means that socio-cultural aspects are labelled inconsistently. Often, conclusions about the considered socio-cultural aspects can only be indirectly drawn from constructs addressed in studies.

In addition to the variety of socio-cultural aspects and methodological issues that need to be considered, HTA in itself is a culturally shaped process. It is implemented in a specific socio-cultural context and involves interaction with the respective institutions, actors and methods. HTA is seen as "a field of knowledge production that is policy purposive" (Williams et al., 2003, p.42), which becomes visible in the "evidence that meets well defined and agreed standards of quality" (ibid) related to a specific cultural rationality. "HTA has been established through a community of practice that defines what acceptable facts about a technology are, and how they should be constructed" (ibid, p.43). In that context, e.g. Williams et al. (2003) show how methodological problems mirror political problems concerning the stabilization of new technologies and clinical practice, and how these problems are to be solved. The reflection on socio-cultural aspects gives an opportunity to critically contrast the normative perspective of traditional HTA, and to question and support the process of HTA as well as the related outputs. It could however also contribute towards the development of HTA to a method that allows for cultural heterogeneity (Stirling, 2008) - with re-

gard to the evidence, stakeholders involved, methods applied etc.

5.1.3 *Description of available approaches to address socio-cultural aspects in HTA*

We consider theory-based approaches as well as methodological approaches which are important to address socio-cultural aspects in HTA.

Theory-based approaches

Theory-based approaches can be relevant a) to shape the HTA in general as well as to shape the understanding of socio-cultural aspects (e.g. what is meant by social inequality?) and b) to frame the assessment of heterogeneous groups' perspectives on specific health technologies and their implementation.

Theory-based approaches in the first sense do already exist in HTA (see chapter 4), but are not explicitly applied to the assessment of socio-cultural aspects. Examples are the Constructive Technology Assessment (e.g. Rip et al., 1995; Schwarz & Thompson, 1990), the socio-cultural Shaping of Technology (Clausen & Yoshinaka, 2004; Jorgensson et al., 2009), and the Interactive HTA (Reuzel, 2004; Reuzel et al., 2001; Reuzel et al., 1999). These approaches underline the importance of socio-cultural aspects in HTA, e.g. for the acceptance and viability of a technology. They frame the understanding of socio-cultural aspects and the idea of mutual interactions between technology and society, and also emphasize stakeholder involvement in HTA.

Theoretical approaches from social and cultural sciences could be of interest for the systematic addressing heterogeneity of different groups in HTA (theoretical approaches in the second sense). Examples that could be applied for such an analysis include Pierre Bourdieu's Habitus concept (Bourdieu, 1977) or the Cultural Theory (Douglas, 1978; Schwarz & Thompson, 1990; Thompson et al., 1990).

In this guidance we use Cultural Theory as an example due to its empirical application²² and because it is closely linked to the Constructive Technology Assessment²³. Cultural Theory – as described in detail in the appendix (see 9.2.3) – presents an option to analyse four different cultural types of organizing social relationships. These elaborated ideal types are hierarchy, individualism, egalitarianism, and fatalism. Each of them de-

scribes how social groups differ in valuing specific aspects related to a health technology (e.g., equal access, risk perception, certainty, and preferences in decision making) and its benefit. Applying these ideal types in HTA could for example show how groups differ in their perception and acceptance of a health technology and why a technology succeeds in the one but fails in another context. The importance of the latter was shown for example by the famous assessment of cochlear implants (Reuzel, 2004). While cochlear implants were assessed as beneficial when addressing deafness as a disease of the ear (in an hierarchical context), at the same time members of the deaf community (an egalitarian context) understood deafness as a central characteristic of their social group and perceived cochlear implants as a threat for the deaf community.

In the presented guidance Cultural Theory is applied to capture different perspectives by combining the socio-cultural framework presented in Figure 10 and the four ideal types of Cultural Theory. The socio-cultural framework presents socio-cultural aspects relevant for HTA such as "the understanding of the health issue", "the perceived usefulness of the health technology" or "the user-professional relationship". All of these categories are reflected upon the four different perspectives (see Table 27 to Table 35). This enables a cultural sensitive analysis which takes cultural diverse preferences e.g. for autonomy, for shared decision making, for medical treatments etc. into account. Further, challenges linked to the implementation of technologies in different socio-cultural contexts can become visible. E.g., challenges linked to the implementation of home based palliative care provided by an egalitarian team (characterized by shared responsibility, a democratic team approach) in the hierarchical setting of a nursing home.

Methodological approaches

One reason given for the underrepresentation of socio-cultural aspects in HTA is the lack of well-developed methods to assess socio-cultural aspects (Busse et al., 2002) – although some approaches are available. In their literature review Lehoux and Williams-Jones (2007) identified three approaches used by bioethics and social scientists: seeking expert advice, primary research using methods of qualitative and quantitative empirical research, and secondary research based on published literature on social and ethical issues. Gerhardus and Stich (2014) summarize four methodological approaches for assessing social aspects of health technologies, which are checklists,

literature reviews, participatory approaches, and primary empirical research. These four methods were confirmed by a systematic literature search conducted for the presented guidance (see 5.2 and 9.2.1). The four methods are presented in the following highlighting their respective advantages and disadvantages.

Checklists for experts

In checklists for experts different aspects are listed and operationalized using a number of questions and sub-questions aiming at an overview of a range of aspects. Checklists are often presented to HTA-developers. They can be used to structure expert consultations (as a kind of interview guide) and literature searches. An example of a checklist addressing socio-cultural aspects in HTA is presented in the HTA Core Model (EUnetHTA, 2015). The socio-cultural framework presented here (see Figure 10) can also be applied as a checklist which combines the identification of several aspects and the reflection on cultural heterogeneity for each framework category.

The effort involved in the completion of such a checklist is manageable. Checklists help structure the assessment and guide the HTA-conductor by using a choice of questions. However, checklists differ in their comprehensiveness, i.e. in the amount of details and the variety of aspects they address, and in their degree of cultural sensitivity. Nevertheless, using a well working checklist offers an option to compare assessments of different technologies. When applying checklists, attention must be paid to the involvement of cultural diversity and the maintenance of openness to additional information. It might be worth adding open questions allowing for additional information as well as to address interrelations between the different parts of the checklist.

Literature reviews:

(Systematic) literature reviews are a systematic tool to identify and synthesize scientific evidence from a range of studies. An example is the systematic review of the socio-cultural, ethical and legal aspects of genetic cancer risk assessment technologies (Kmet et al., 2004). Literature

searches are common in HTA-agencies. They are applied as an efficient tool HTA-conductors are familiar with.

For all kinds of reviews the key principles of systematic reviewing as described by Snilstveit et al. (2012) apply as well as the systematic steps such as the focus on predefined inclusion and exclusion criteria as emphasized by Saini and Shlonsky (2012). Before conducting a literature review, its objective has to be explicitly stated. There are "different types of reviews for addressing different types of questions" (Snilstveit et al., 2012) and purposes (Grant & Booth, 2009). Depending on the research question, the sources of information will also differ. "To answer questions such as 'why' an intervention works (or not), or 'how' something works, qualitative research and surveys would be more appropriate than experimental and quasi experimental studies" (Snilstveit et al., 2012). Socio-cultural aspects are often addressed in qualitative studies aiming at describing of issues and meanings of concepts (Berg, 2009). These differ from quantitative studies in their presentation and quality criteria (Ring et al., 2011b).²⁴

"If a systematic review aims to answer several questions, researchers might need to draw on a range of different types of evidence" (Snilstveit et al., 2012). If different types of evidence have to be synthesized narrative review approaches such as content analysis, thematic summaries, framework or thematic synthesis, realist synthesis or meta-ethnography can be used (Snilstveit et al., 2012). The strengths and weaknesses of these methods are presented elsewhere (e.g. Ring et al., 2011a; Snilstveit et al., 2012). For complex technologies the "realist review" (Pawson et al., 2005), which takes context and implementation of a technology into account, could be an option.

Literature reviews addressing socio-cultural aspects should include socio-cultural and psychological databases in addition to medical and pharmaceutical databases. Examples of the variety of databases are: MEDLINE, EMBASE, BIOSIS Previews, CINAHL, PsychInfo, Science Citation Index Expanded, Socio-cultural Sciences Citation Index, Arts & Humanities Citation Index and the Databases of the Cochrane Library (Database of Abstracts of Reviews of Effects, National Health Service Economic Evaluation Database, Health Technology Assessment Database, Cochrane Methods stu-

22 Please find various examples e.g. on family structures and national political cultures in (Mamadouh, 1999) or consumption styles (Dake & Thompson, 1999) in issue 4 (47) of the GeoJournal (1999).

23 Constructive Technology Assessment (CTA) represents a paradigm of technology assessment that aims at a broader understanding of technology implementation and development. CTA emphasizes the cognition that technology assessment has to be shaped as a continuous process, has to involve the interaction between technology and the socio-cultural context it is supposed to be implemented in (in both directions), and also makes clear that the public has to be involved in the assessment process (Freeman, 1995) Understanding the interactions between technology and its socio-cultural embedding are linked with improving its socio-cultural acceptance, its viability and the development of new technologies. This leads to the necessity of considering public opinion, i.e. users and communities, at different stages of the assessment process (e.g. during the development of the technology or the conceptualization of the technology). "For the OECD, the term 'constructive' indicates the expectation of minimizing mismatches, wrong investments and possible socio-cultural conflicts, which one can read as a version of our general formulation of constructive technology assessment" (Rip et al., 1995, p.6). Technology assessment in this sense is understood as a socio-cultural learning process (Rip et al., 1995; Schwarz & Thompson, 1990; Wynne, 1995) and as a socio-cultural process of decision-making. Therefore it is important to know exactly which socio-cultural conditions influence the technology's viability (e.g., (socio-cultural) risk perceptions of different groups of people such as experts and lay people).

dies, Cochrane Reviews, Cochrane Technology Assessment). Hand searches in journals highly relevant to the research question or perusing reference lists of identified articles can also be of advantage. A chapter on systematic literature research for socio-cultural aspects in HTA is currently being developed for the HTAi vortal (SuRE Info²⁵).

To capture a variety of heterogeneous perspectives the inclusion of grey literature can be advantageous. Although they have less scientific evidence quality, websites, newspapers, or documents from different stakeholder groups such as professional umbrella organizations can be of interest to reconstruct different perspectives regarding a technology and its acceptance.

Difficulties conducting literature reviews occur if the evidence base is scarce, which is often the case with regard to socio-cultural aspects of health technologies. The quality of the studies available could also lead to problems often related to sampling (Kmet et al., 2004).

The socio-cultural framework provided in this guidance can be applied to structure the collected evidence, and also to deliver search specific search terms regarding socio-cultural aspects.

Participatory approaches:

Participatory approaches such as the Interactive HTA and the Social Shaping of Technology, aim at ensuring legitimacy of decisions, transparency of perspectives and at improving the relevance of research. Participatory approaches, stakeholder involvement or the involvement of the public²⁶, respectively include the perspectives of different stakeholders and their priorities in HTA. This could help to focus the assessment more on user values – a rationale that is made by several authors (e.g., Gagnon et al., 2011; Gauvin et al., 2010) and therefore improve the acceptance by different stakeholder groups (Bridges & Jones, 2007; Pizzo et al., 2014).

As shown for example by Abelson et al. (2007), HTA-agencies differ in the way and the models they choose to involve stakeholders and the public in HTA. In addition, models cannot be easily transferred from one national context to another (Abelson et al., 2007; Cavazza & Jommi, 2012). For example, challenging questions are how and when stakeholders with different experiences in HTA, different interests as well as with different levels of influence

on decision making processes (e.g. representatives of industry, of national health care agencies, local government representatives, clinicians, patient associations) should be involved (Abelson et al., 2007; Cavazza & Jommi, 2012).

Participatory approaches involve stakeholders differently. Abelson et al. (2007) offer a framework presenting different roles of stakeholders and levels of involvement. Gagnon et al. (2011) distinguish between active participation, consultation and communication/information and link these approaches to corresponding methods. Objectives of stakeholder involvement can be to receive or seek information, to provide data, to comment, to appeal, to collaborate, to control (Gauvin et al., 2010), to identify assessment topics, to prioritize or to validate assessment results. Stakeholder consultations could be done during workshops, or during individual or group consultations. They can be conducted as advisor consultations or qualitative research. Examples of participatory methods are the Delphi method (Dalkey & Helmer, 1963; Delbecq et al., 1975; Linstone & Turoff, 1975; Sackman, 1974) and the Nominal group technique (Delbecq & Van de Ven, 1971; Delbecq et al., 1975). These methods have been applied in HTA for instance by the Citizen Council of the National Institute for Clinical Excellence (NICE) (National Institute for Clinical Excellence, 2008). Another example is the interactive evaluation (Reuzel et al., 2001) which was conducted for the assessment of cochlear implants (Reuzel, 2004). Frank Fischer's (Fischer, 1995) approach to "place normative inquiry on an equal footing with empirical analysis" is another example for applying a participatory approach in evaluations. It can serve as a framework to include results of participatory evaluations.

Participatory approaches are advantageous in capturing heterogeneous perspectives. Professionals, patients, relatives etc. are involved as experts in using the technology. At the same time the choice of participants is a critical point and could lead to bias. Difficulties in ensuring a balanced stakeholder sample across stakeholder groups have been shown (Nielsen et al., 2009). Additionally, the consideration of heterogeneity often focuses on different stakeholder groups such as patients, professionals, relatives. Socio-cultural differences between stakeholders within one group are rarely

²⁴ Detailed guidance on the use of qualitative data in HTA is presented in another INTEGRATE-HTA guidance (see Booth et al. 2016).

²⁵ <http://vortal.htai.org/?q=sure-info>, accessed 2nd June 2015

²⁶ Although often used interchangeably, the terms 'stakeholders' and 'the public' are not the same thing. Stakeholders, as the term suggests, are parties that have a 'stake' (self-interest in terms of resources, power, etc.) in a given issue (e.g., professional, consumer advocacy groups and pharmaceutical companies). Technically, the public also holds a stake on many issues, but representing the public's interest incorporates a much broader, diffused and fragmented set of interests that are not easily mobilized" (Gauvin et al., 2010).

addressed though. Group dynamics and socio-cultural differences can however also cause misunderstandings, social desirability, and scepticism against research. Stepwise stakeholder involvement as suggested in the socio-cultural assessment process (see Figure 11), which increases the level of heterogeneity and uses information from earlier consultations as a base for the discussion, could ease the situation.

Differences in the understanding of the technology itself could also cause misunderstandings. The researchers' definition of the technology does not necessarily represent the understanding professional providers have. To ensure a common understanding, the technology should be defined at the beginning of each stakeholder meeting. Differences should be identified and clarified whenever relevant.

HTA-agencies decide about stakeholder involvement on a case-by-case basis (Abelson et al., 2007). According to Abelson et al. (2007), HTA-agencies often give limited resources, but also fears of losing control and power as reasons for non-improving stakeholder involvement. HTA-agencies, especially those with a positivist paradigm, also express fears of creating unscientific evidence while others understand HTA as a value-laden process and emphasize a participatory approach (Gauvin et al., 2010).

Primary studies using methods of empirical research

Socio-cultural aspects of health technologies in HTA can be considered through primary research, applying both quantitative and qualitative methods of empirical research. Examples are surveys (e.g. Nigenda et al., 2003) or interview studies (e.g. Bardia et al., 2004), as well as studies using mixed methods approaches as used e.g. in TA-SWISS (2001). In the latter, face-to-face interviews, interviews by phone and also a postal questionnaire were used. Qualitative methods are of advantage when attitudes, acceptance or background theories of stakeholders are of interest.

Primary research entails high expenditure regarding designing and conducting research. Therefore the choice of primary research should be carefully deliberated. If primary research is conducted, the socio-cultural framework can be used as a tool to develop research instruments such as questionnaires, interview guidelines or observation protocols.

5.1.4 Complexity and integrative perspective

All technologies are, at varying degrees, complex and/ or are operating within complex systems. Many of the traditional methods of analysis in HTA rely upon strong assumptions regarding the structure, content and objectives of a technology, its implementation, the system within it is intended to act, and the potential interplay and co-evolution of the system and the technology. In an HTA the question is if the complexity of a health technology is relevant for the socio-cultural assessment. Therefore, the synthesis developed for the identification of components of complexity for moral issues (see 4.1.3) and Table 1 provide the starting point for the socio-cultural assessment. In addition, the framework for the assessment of socio-cultural aspects (see 5.2) offers a comprehensive tool to identify and operationalize socio-cultural aspects relevant in HTA. It integrates a variety of aspects on different levels of social organization and from the perspectives of social and cultural diverse groups.

5.2 GUIDANCE DEVELOPMENT

The guidance on the assessment of socio-cultural aspects in HTA comprises an assessment process (see Figure 11) including five assessment steps and a socio-cultural framework which can be applied to steps 2 to 5. Step 1 is added at the beginning of the assessment, should the question of complexity be of relevance in the HTA (see Figure 11).

To develop the guidance for socio-cultural analysis in HTA different preparatory investigations were necessary:

- a) Identification of methods to address socio-cultural aspects in HTA: The assessment process (Figure 11) was developed taking stakeholder involvement, priority setting and available methods to assess socio-cultural aspects of health technologies into account. To identify the latter we conducted a literature review (see 9.2.1, publication in preparation). In addition, we searched for all documents on HTA-methodology presented on the websites of the INAHTA-agencies up to September 2013. We also contacted the respective agencies by email to find out, whether they address socio-cultural aspects in HTA, and if yes, how they do this (see 9.2.2). The identified methods – checklists, lite-

literature searches, participatory approaches and primary research - are described above (see 5.1.3).

- b) **Categorization of socio-cultural aspects addressed in HTA:** To develop a common understanding of socio-cultural aspects we extracted the socio-cultural aspects addressed in the publications identified from our literature review described under a). These aspects were categorized by an open coding procedure inspired by Grounded Theory (Strauss & Corbin, 1990). We identified three main categories: 1) the social construction/ understanding of the health issue, 2) the social image/ understanding of the health technology, and 3) socio-cultural aspects of implementation and organisation (see Figure 10). Categories 2 and 3 have further sub-categories. A detailed description of all categories, operationalized questions for their application in HTA, and examples from applying the framework in the case study on models of (reinforced) home based palliative care (HBPC/ rHBPC) are presented in the following sections (see Table 16 to Table 26).
- c) **Reflection of cultural heterogeneity:** For capturing cultural heterogeneity we used Cultural Theory as an example. Cultural Theory is a common approach in political science, which identifies four cultural types that differ in their way of organizing social relationships (see 9.2.3). To capture heterogeneity, we reflected on each category as found in point b) against the background of each cultural type. These type-specific descriptions (see 9.2.4) can be used to analyse socio-cultural aspects from different cultural perspectives.

The categories presented in Figure 10 are described in Table 16 to Table 26. The assessment process, including the socio-cultural framework, was applied in the case study on reinforced models of home based palliative care (rHBPC) in order to revise and refine the framework.²⁷ Some of the case study results are used as examples to help explain the application of the framework for each (sub-)category.

²⁷ Additional information is presented in the case study on HBPC and rHBPC (see Brereton et al., 2016).

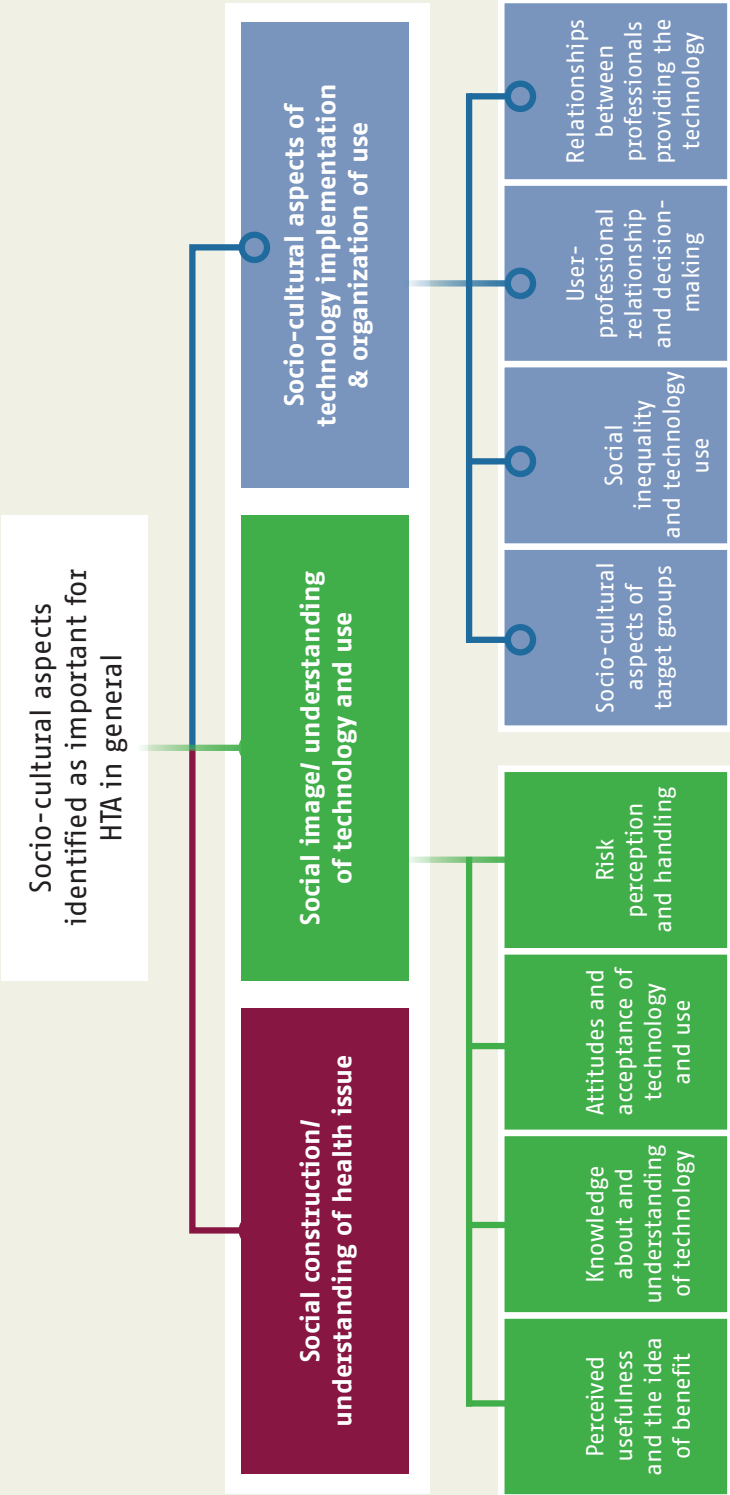


Figure 10: Overview of the socio-cultural aspects represented in the socio-cultural framework.

Table 16: Framework main category: Social construction/ understanding of health issue.

Aspect of interest for socio-cultural assessment:	Social construction of health issue/ understanding of health issues the technology addresses
Description of aspect of interest:	<p>How people see and experience health and related phenomena is based on the socio-cultural context they live in. Health knowledge and definitions of diseases are always related to a certain cultural context. Different ideas (also regarding different treatment options) exist next to each other. There are different normative perspectives of how certain groups deal with health issues and their treatment. This influences the design of health technologies. The way individuals, a group or a whole society defines/ perceives a health issue influences how and for what purpose a technology will be developed, assessed, used, and implemented. Various diseases and health conditions may have different social status and prestige, and technology can influence the social status and prestige of diseases and health conditions.</p> <p>Technologies in themselves can also change the way in which health issues are socially defined. Examples are technologies' influence on the definition of cerebral death or the conceptualization of an embryo. Increased use of ultrasound technology during pregnancy for example changed the concept of risk and the related necessity of control provided by medical experts. In this example technological developments such as ultrasound technology influence the public's ideas of pregnancy. Individuals who refuse prenatal screening could be confronted with discrimination and stigmatization (e.g., accusations of not taking responsibility, being an uncaring mother).</p>
Possible questions to address/ operationalize the framework category:	<ul style="list-style-type: none"> • How is the health issue conceptualized in different cultural contexts? • How do different stakeholders (e.g. professionals, patients, relatives) describe the health issue of interest? • How has the understanding of the health issue/ different perspectives of it changed historically? Were different (political) groups involved? • Which understanding of the health issue is represented in the technology of interest? Did the technology influence/change the way the health issue is seen by different groups? • Which definition of the health issue is generally agreed on/ legitimized and institutionally supported, e.g. in treatment options? • How do patients/informal caregivers and professionals deal with or experience the health issue? • Does the introduction of the technology professionalize/ medicalize the handling of the health issue? • What is the status and the prestige of the health status, and how is this changed by technology?
Example: The socio-cultural image/ understanding of HBPC	<p><i>Health issue is understood as a "journey"</i></p> <p>HBPC characterizes the health issue as a "journey" (the dying process). The "journey" consists of phases/ transition points characterized by changing support needs. Professionals guide patients and their relatives through the process, preparing and advising them. This approach is different to curative health services, which focus on specific diagnosis and related treatment options. The unspecific focus "end of life care" can lead to uncertainties related to access to HBPC.</p> <p><i>The holistic perspective of health issues</i></p> <p>The holistic approach emphasizes that the diagnosis should not play a central role when defining the health issue (although diagnosis can decide about access to HBPC). HBPC holistically addresses the physical, psychological and social needs of the patient (e.g. pain seen as bio-psycho-social phenomenon, cannot be treated only with pain killers). Focusing on medical pain management without taking other components into account is criticized in HBPC. Furthermore, health issues/needs should be defined by the patient. Hence a general practitioner's (GP) referral of a patient to HBPC with the aim to reduce physical pain can be questioned from the HBPC-team, because pain reduction does not have to be the patient's main problem.</p>

Table 17: Framework main category: Social image of technology and use.

Aspect of interest for socio-cultural assessment:	Social image of technology use
Subordinated aspects:	<ol style="list-style-type: none"> 1. Perceived usefulness and the idea of benefit 2. Knowledge about and understanding of technology 3. Attitudes to and acceptance of technology and use 4. Risk perception and handling <p>The four subcategories are described in separate tables (see Table 18 to Table 21).</p>
Description of aspect of interest:	Technologies and ideas of health and illness are mutually linked social constructions, produced and confirmed by social actions. As such, a technology is influenced by cultural and social norms, values and expectations linked to the health issue and vice versa. These values, norms, and expectations influence how, when and for what purposes a technology is/ will be designed and implemented. They affect which aspects are prioritized and which stay hidden. Treatment alternatives or alternative ways of shaping a technology could be overlooked if cultural heterogeneity is not taken into account.
Possible questions to address/ operationalize the framework category:	<ul style="list-style-type: none"> • What is the symbolic meaning and social status of the technology for different cultural groups? • Which aspects do representatives of different groups perceive as important? • Do specific groups refuse the application of the technology? If yes, why? • Which understanding of health issue is represented in the technology of interest? (How does it influence the implementation process?)
Example: The socio-cultural image of using HBPC	<p><i>Associations with HBPC</i></p> <p>HBPC in England focus on the end of life. This gives a frame of the period in which services are provided. The idea is to accompany the "last journey" in a holistic way to ensure patients' quality of life as much as possible. Getting a referral to HBPC can be very challenging due to patients' and relatives' associations and expectations. To ensure a realistic picture of what the services can offer, HBPC-professionals discuss the idea of HBPC for each individual case together with patients and relatives.</p> <p><i>Home as the best place to die vs. economization</i></p> <p>HBPC is linked to the idea that "home is always the best place to die", which challenges the patient-centred approach. This approach demands that a decision has to be taken based on an individual case and that changing needs to be taken into account. Although there are benefits such as familiarity with the situation at home, stakeholders expressed concerns regarding the potential (economic) misuse through pressuring people to die at home. These concerns were based on the assumption that hospital care or hospice care would be more expensive than HBPC – given the number of unpaid informal caregivers for example.</p>

Table 18: Framework subcategory: Perceived usefulness and the idea of benefit.

Aspect of interest for socio-cultural assessment:	Social image of technology use
Subordinated aspects:	1. Perceived usefulness and the idea of benefit 2. Knowledge about and understanding of technology 3. Attitudes to and acceptance of technology and use 4. Risk perception and handling
Description of aspect of interest:	<p>The category "perceived usefulness and the idea of benefit" refers to the evaluation of a technology. Understanding and evaluation of a technology are culturally influenced. This includes various preferences for outcome measures and differences in the understanding of effectiveness and safety. Furthermore, HTA as an assessment procedure is itself culturally shaped.</p> <p>The category can be considered from different stakeholders' perspectives, e.g., political decision makers, providers and technology users (also see Table 23). It refers to decision-making processes regarding the implementation of a technology in general (conditions that have to be fulfilled, responsibilities etc.) as well as in concrete treatment situations, where expectations of users and service providers have to be negotiated (see also Table 25). In both cases culturally diverse ideas of benefit and evaluation processes can lead to misunderstandings and bias the assessment, if heterogeneity is not taken into account.</p>
Possible questions to address/ operationalize the framework category:	<ul style="list-style-type: none"> • Which aspects/ outcomes do stakeholders describe as being important regarding the technology of interest? • How do different groups consider the benefit of the technology? Who defines the benefit of the technology, and how is that done? How are the patients' perspectives involved in defining the benefit of the technology? • Do professionals/ patients/ relatives differ in the aspects they consider to be important when talking about or evaluating the technology? If yes, how and why do they differ? What do they consider as problems/ disadvantages/ advantages for patients/ relatives/ professionals, etc.? • What are the (culturally different) preferences and priorities of 1) political decision makers and 2) patients and providers? How are differences handled politically? • When do stakeholders evaluate the technology as being successful, and how does this differ among stakeholders?
Example: The socio-cultural image of using HBPC	<p><i>Benefits of HBPC/rHBPC for patients, relatives and professional providers</i></p> <p>HBPC addresses the family as a unit. Consequently benefits need to be described for patients and informal caregivers. When receiving HBPC/rHBPC relatives can be closer to their family members and manage their own lives more easily (e.g. no need to rush into a hospital). rHBPC offers specialized services to support relatives such as a sitting service that allows for some free time or social activities to protect caring relatives from the risk of social isolation. rHBPC prepares relatives as part of the patients' "journey" and may extend into the bereavement phase. However, relatives might be empowered in a way that is no longer beneficial to the patients, e.g. if the reflection on the relatives' own position leads to conflicting wishes/needs of patients and informal caregivers, which can result in giving up the caring role.</p> <p><i>Benefit assessment of HBPC</i></p> <p>The variety of perspectives involved in HBPC (e.g., different professional cultures, heterogeneity of patients' preferences) challenges the way benefit is defined. Furthermore the understanding of HBPC can differ between (different) service providers and decision makers. Helping the patient to discover a meaning of life in the presence of incurable fatal disease was considered as a key outcome by many professional providers. Others however emphasize medical pain management.</p>

Table 19: Framework subcategory: Knowledge about and understanding of technology.

Aspect of interest for socio-cultural assessment:	Social image of technology use
Subordinated aspects: (separate description)	<ol style="list-style-type: none"> 1. Perceived usefulness and the idea of benefit 2. Knowledge about and understanding of technology 3. Attitudes to and acceptance of technology and use 4. Risk perception and handling
Description of aspect of interest:	<p>Knowledge is socially constructed. What is considered as "the right" knowledge and how it is legitimized is socially negotiated and can differ between groups. Knowledge about a particular technology influences its social image. Understanding the purpose of a technology basically shapes decision-making at the political level as well as in concrete treatment situations. This framework category encompasses the value that is assigned to new technologies and their implementation, user ideas, ideas that influenced the technologies' development, and knowledge about treatment alternatives in comparison to the technology of interest.</p>
Possible questions to address/ operationalize the framework category:	<ul style="list-style-type: none"> • Which kind of knowledge is perceived as a legitimised basis of the assessment (medical vs. psychosocial knowledge, qualitative vs. quantitative research, lay peoples' expertise vs. professional expertise)? • Is there (socio-culturally) accepted standard knowledge decision makers refer to? (If they refer to expert knowledge: who is considered to be an expert)? • Are different kinds of knowledge integrated in the assessment? • Which knowledge legitimizes the use of the technology? (Is there contradicting information in culturally different groups?) • Does the technology promote specific kinds of knowledge?
Example: Knowledge about and understanding of HBPC	<p><i>Understanding and expectations of patients and relatives related to HBPC</i></p> <p>Knowledge and understanding are keys to being confident with the services and the situation in HBPC. HBPC and rHBPC comprise a variety of services often not known by patients and informal caregivers. To obtain a common level of understanding from the beginning, professionals should find out how much patients' and relatives' understand about HBPC. Professionals should also inform patients and relatives about the available services at the beginning of HBPC because patients/relatives tend to ask more about specific services they know can be accessed than which services are part of HBPC. This task should be repeated if needs change during the "journey". Informal caregivers who coordinate the care, report about "battles" to get information and funding.</p>

Table 20: Framework subcategory: Attitudes and acceptance of technology and use.

Aspect of interest for socio-cultural assessment:	Social image of technology use
Subordinated aspects: (separate description)	<ol style="list-style-type: none"> 1. Perceived usefulness and the idea of benefit 2. Knowledge about and understanding of technology 3. Attitudes to and acceptance of technology and use 4. Risk perception and handling
Description of aspect of interest:	<p>An attitude is a summative assessment of a person, group, or the public assessing the technology at a certain point in time. Attitudes are related to beliefs about science, social trust, perceptions of benefit and risks of a technology. They express fears, hope, curiosity, and security ideas that are linked to the technology of interest. Attitudes towards a technology characterize its social image. They are influenced by knowledge about the technology, the perceived usefulness as well as by socio-demographic variables such as gender and age. They are also part of the social and cultural context of users, providers and decision makers. The receptiveness of the users, providers and decision makers to new technologies or fashions (e.g. of diagnoses) transfers into attitudes. Refusal and acceptance are consequences of attitudes associated with a technology. Non-acceptance can be a consequence of user dissatisfaction, but also of culturally non-sensitive information. Acceptance can be analysed from the perspective of users, providers, decision makers and the public. Attitudes can change through learning processes (e.g. working with a technology can change a provider's attitude and lead to different management decisions).</p>
Possible questions to address/ operationalize the framework category:	<ul style="list-style-type: none"> • Under which circumstances do (socio-culturally different) decision makers/ users/ providers trust in or accept the technology of interest? • Why does the technology work/is accepted in one cultural context and not in another? • Why do people refuse to use a technology? • What do providers/ political decision makers/ patients/relatives think about the technology (e.g. advantages/disadvantages, different perspectives, topics that are controversial, problems, successes)? • Does the technology fit into the structures of the health system, or does it challenge it?
Example: Attitudes and acceptance of HBPC	<p>Attitudes against HBPC are influenced by background ideas of the purpose of HBPC and related health services (see also Table 17). E.g., expectations towards HBPC might differ depending on whether informal caregivers view professional services as a support to fulfil the caregiver role, or if they see them as the responsible care providers. Additionally attitudes to care providers are influenced by stereotypes related to the services itself (e.g., suspicion about social care).</p> <p>HBPC is based on societies' ideas about accompanying dying people. Professionalization in HBPC will influence these ideas and the ideas will also change HBPC. The symbolic value of HBPC for patients and caregivers correlates with the acceptance of the care situation by family and friends. The cultural context shapes HBPC (e.g., people living in an area with strong social networks and social support will have different attitudes towards HBPC than those living in an area characterized by anonymity and individuality). The cultural background also influences role expectations (as a patient or an informal caregiver) (e.g., an area highly valuing family support could socially consider taking over the role of an informal caregiver as a duty, especially for women). HBPC can change these perspectives e.g. through the empowerment of informal caregivers. However, this can also challenge the informal caregiver's position as a member of the given socio-cultural environment. For instance, the question whether it is acceptable to stop caring depends on the expectations related to the caregiver role.</p>

Table 21: Framework subcategory: Risk perception and handling.

Aspect of interest for socio-cultural assessment:	Social image of technology use
Subordinated aspects: (separate description)	<ol style="list-style-type: none"> 1. Perceived usefulness and the idea of benefit 2. Knowledge about and understanding of technology 3. Attitudes to and acceptance of technology and use 4. Risk perception and handling
Description of aspect of interest:	<p>"Risk perception and handling" refers to culturally different definitions and perceptions of risk and the corresponding ways to handle these (Beck, 1992). Risk assessment usually focuses on non-desired consequences of a technology's implementation. However, risk can also be seen as a chance for development. These two ways of seeing risk lead to different approaches of technology assessment (Schwarz & Thompson, 1990). While one tries to anticipate and control all consequences of technology use, the other deals with risks when they appear by reflecting on the experiences (ibid.). Stakeholder involvement is essential to identify issues relevant for people involved in technology-related processes.</p>
Possible questions to address/ operationalize the framework category:	<ul style="list-style-type: none"> • Do different groups perceive risks related to the technology differently (e.g. the risk of personality changes associated with Deep Brain Stimulation in patients with Parkinson's Disease)? • How do different groups define and handle risks? • Which ideas of safety come up in different groups? • Does the way risk is defined or perceived lead to overdiagnosis and medicalisation? • Does the technology change health behaviour such that a riskier behaviour is expected e.g. because people feel more secure due to the technology (HIV/AIDS prevention)?
Example: Knowledge about and understanding of HBPC	<p>A risk for the successful provision of HBPC is associated with the number of agencies involved in the care. This is not only due to a lack of coordination and cooperation, but also to different care approaches and training standards. There are also differences in perceived risks associated with hospitalisation of patients at the end of their life (inappropriate treatment, overtreatment).</p> <p>There is a risk of overburden and social isolation for informal caregivers as well as the risk of injury that might occur due to wrong handling of the patient. Therefore, professionals recommend that informal caregivers need a backup system (e.g., if own health problems arise).</p> <p>Professionals delivering HBPC could become co-dependent through being too involved in the complex care situation. Accordingly, professionals have to explicitly communicate to patients and families that HBPC is delivered by a team.</p>

Table 22: Framework main category: Socio-cultural aspects of implementation of technology /organization of technology use.

Aspect of interest for socio-cultural assessment:	Social image of technology use
Subordinated aspects: (separate description)	<ol style="list-style-type: none"> 1. socio-cultural characterisation of target group 2. social inequalities and technology use 3. user-professional relationships and decision-making 4. relationships between professionals providing the technology <p>The four subcategories are presented in separate tables (see Table 23 to Table 26).</p>
Description of aspect of interest:	<p>"Socio-cultural aspects of implementation" focus on characteristics of the target group, social inequalities, the relationship between user and professional provider, decision-making in the concrete treatment situation and relationships between different professionals providing the technology.</p>
Possible questions to address/ operationalize the framework category:	<ul style="list-style-type: none"> • What is the organizational (socio-cultural) context for which a technology is developed/ in which it is implemented? • Could the introduction of the technology reinforce existing inequities (e.g., in the case of prevention of cervical cancer)? • Can the technology be transferred from one socio-cultural context to another? If yes, under which circumstances?
Example: socio-cultural aspects of implementation and organization of HBPC	<p><i>HBPC challenges the health system</i></p> <p>HBPC includes a variety of services which are continually developing. This variety combines different approaches/ cultures of care. An example is the link between clinical health and community health care and social care, which are related to different care priorities and foci (see also Table 17).</p> <p>HBPC appears to be a fast developing area of services which struggles to bring egalitarian ideas in a non-institutionalized care context. This egalitarian approach of care could influence the health care system and make changes necessary. Or, the other way round, HBPC might need to be put in the established care structures, which could challenge its egalitarian ideas, thereby changing the shape of the technology.</p>

Table 23: Framework subcategory: Socio-cultural aspects of target group.

Aspect of interest for socio-cultural assessment:	Social image of technology use
Subordinated aspects: (separate description)	1. socio-cultural characterisation of target group 2. social inequalities and technology use 3. user-professional relationships and decision-making 4. relationships between professionals providing the technology
Description of aspect of interest:	<p>The characterisation of the target group of the technology is important in understanding compliance and refusal of treatment and how the family is affected by the technology. Beyond this, ideas (inner-stereotypes) of (future) users influence the design and development of a technology.</p> <p>Target groups are often characterised by a set of socio-demographic variables such as age, gender, educational level, race, ethnicity, religion etc. The characterisation by socio-cultural context and taking the social network and related aspects into account could be advantageous when describing the target group of a technology. Information about family roles and related expectations, the idea of being a patient, or the way the social support network functions help to understand whether and why technologies fail, or succeed in a specific cultural context.</p>
Possible questions to address/ operationalize the framework category:	<ul style="list-style-type: none"> • What are the socio-cultural characteristics of the target group? • Do aspects such as age, gender, educational level, race and ethnicity, religion of patients and their relatives play a role in the technology of interest? If yes, in which way? • How does the social network (family, friends) of users affect the application of the technology and vice versa? • How do patients and informal carers describe their role in the family and treatment situation? • What are the preferences of different target groups (e.g. for information, decision-making, shaping the patient role etc.)? • Do different cultural contexts of users influence how they refer to the technology? If yes, how and why? • How do different socio-cultural groups evaluate the refusal of a technology (e.g., social desirability and culturally desired ways of treatment)?
Example: Socio-cultural aspects of the target group in HBPC	<p><i>Differences between patients/families</i></p> <p>With regard to the socio-economic status and the level of education, less affluent areas are described as having the greatest family support. Education level is more diverse in areas with less family support. Higher education level is associated with more requests for information and higher expectations of the services. The majority of informal care givers is provided by females. Looking at the socio-demographic development, it is mentioned that informal care givers are becoming older, which may result in a worse health status.</p>

Table 24: Framework subcategory: Social inequality and technology use.

Aspect of interest for socio-cultural assessment:	Social image of technology use
Subordinated aspects: (separate description)	<ol style="list-style-type: none"> 1. socio-cultural characterisation of target group 2. social inequalities and technology use 3. user-professional relationships and decision-making 4. relationships between professionals providing the technology
Description of aspect of interest:	<p>A technology's implementation and use is linked to questions of social inequality. Social inequality refers to disparate distribution of material and immaterial resources in a society and its consequences for social participation. It is linked to issues of stigmatization and discrimination. The focus is on disadvantaged groups e.g. in accessing the services. Besides this, discrimination can take place if a technology addresses its target group as an entity, without considering different needs.</p> <p>Usually socio-demographic variables such as gender, age, race, ethnicity, economic, and educational status are used to address social inequality. Furthermore, the socio-cultural context of people contains different perspectives on social inequality itself, including differences in handling and valuing it (Schwarz & Thompson, 1990).</p>
Possible questions to address/ operationalize the framework category:	<ul style="list-style-type: none"> • Does the implementation/use of a technology lead to social inequalities (e.g., regarding socio-demographic variables, cultural context or diagnosis)? • Do patients/relatives experience any difficulties in accessing the technology? If yes, how and why do they experience difficulties? How do service providers, politicians etc. view this? • Does the technology lead to any discrimination or change the social status of users? • Are social inequalities evaluated differently in different cultural contexts? • How do different cultural groups value the refusal of a technology? • How do different professionals (e.g. service providers, political players etc.) view existing differences in accessing the technology? Are there different perspectives?
Example: socio-cultural aspects of implementation and organization of HBPC	<p>The egalitarian idea of HBPC is related to ideas of equity. Social inequalities regarding disadvantages in accessing HBPC can be brought to light. Reasons for differences in access are: 1) cultural stereotypes (e.g. some ethnic groups care for their own family at home), 2) scarcity of providers, 3) resource constraints, 4) (lack of) knowledge of services (information is often found on the internet – influence of educational level and health status), 5) local infrastructure, 6) focus on specific diagnosis, 7) the availability of a social support network, 8) continuity of services, 9) non-cancer diagnosis, or 10) living in residential and nursing homes. In addition families differ in their ability to deal with the stress of seeking support, which is also related to specific competencies.</p> <p>Furthermore, the individualized approach of HBPC appears to involve inequalities of care legitimized in the different individual needs of patients. To ensure equality HBPC providers emphasize that strategy of taking more time and resources for disadvantaged people when providing HBPC be followed.</p>

Table 25: Framework subcategory: User-professional-relationships and decision making.

Aspect of interest for socio-cultural assessment:	Social image of technology use
Subordinated aspects: (separate description)	<ol style="list-style-type: none"> 1. socio-cultural characterisation of target group 2. social inequalities and technology use 3. user-professional relationships and decision-making 4. relationships between professionals providing the technology
Description of aspect of interest:	<p>Relationships between users and professionals are embedded in an institutional (socio-culturally shaped) context. These relationships are more or less formally shaped and, include more or less prescribed roles linked to different expectations of autonomy and responsibility. Professionals and professional cultures involved in treatment and decision processes should be described in the socio-cultural assessment. Mutual expectations will influence the way treatment is provided. For instance, ideas of authority and autonomy have to be in accordance with each other to ensure successful treatment. Users and providers socially negotiate to see if their ideas are compatible or if the socio-cultural (institutional, respectively) context of treatment needs to be changed.</p> <p>How the user-professional-relationship is shaped and what that means for the culture of decision-making is closely linked to attitudes regarding a technology and its perceived usefulness, as evaluated by patients and professionals (see also Table 18). Patient preferences for treatment, treatment outcomes (e.g. priorities about daily activities), for counselling and support, as well as treatment ideas of significant others influence the user-professional-relationship.</p>
Possible questions to address/ operationalize the framework category:	<ul style="list-style-type: none"> • What can you say about the relationship between professionals providing the services and their patients and relatives? (E. g. mutual expectations, role pictures, communication, difficulties, important aspects of decision-making, ...) • Which different shapes of that relationship become visible? • Are difficulties using the technology based on different expectations of professionals/ users?
Example: The user-professional-relationship and decision-making in HBPC	<p><i>Degree of intimacy between professionals and users</i></p> <p>Patients and relatives in (x)HBPC share not only their physical symptoms with the professionals, but also stories. In addition, there is no time for patients and relatives to become acquainted with the processes of the health system. Professionals function as empathetic gatekeepers to services and equipment. The user-professional-relationship is characterized by intensive contact and communication. This can result in a close relationship that can be easily misunderstood by patients and relatives as a kind of friendship. Finally, it can become a burden for professionals if they are involved in a complex care situation.</p> <p><i>Decision making</i></p> <p>The culture of decision-making influences whether patients and carers are used to making their own decisions or if they wish for authority. In addition, professionals experience difficulties when applying the patient centred approach due to their socialisation as being professional experts. The hierarchical institutional context (e.g. in a nursing home) can challenge autonomous decision-making.</p>

Table 26: Framework subcategory: Relationships between professionals providing the technology.

Aspect of interest for socio-cultural assessment:	Social image of technology use
Subordinated aspects: (separate description)	<ol style="list-style-type: none"> 1. socio-cultural characterisation of target group 2. social inequalities and technology use 3. user-professional relationships and decision-making 4. relationships between professionals providing the technology
Description of aspect of interest:	<p>Relationships between different professionals providing a particular technology or deciding about it are embedded in a socio-cultural context. This becomes visible in different working cultures, professional cultures, ideas of (interdisciplinary) cooperation, questions of social status and related responsibilities, mutual expectations, as well as in issues of social power in treatment decisions etc. Perceptions of the health issue and the technology are influenced by this context. Technologies that allow physician assistants and nurse practitioners to provide services relatively independently of MDs, such as photodynamic therapy in the treatment of PTT with cell carcinoma, cystoscopy etc. can be examples showing how the use of a technology influences the professionals' status.</p>
Possible questions to address/ operationalize the framework category:	<ul style="list-style-type: none"> • What can you say about the relationship between professionals providing the services and their patients and relatives? (E. g. mutual expectations, professional cultures, role models, communication, difficulties, important aspects of decision-making etc.) • How do different professional cultures influence the provision of the technology (e.g. different views of interdisciplinarity, cooperation styles, team structure, status, and responsibility)? • How should the team structure/ cooperation mode be changed if the technology is transferred to another context?
Example: relationships between professionals providing HBPC	<p><i>Cooperation in a multi-professional context</i></p> <p>HBPC is delivered by a multi-professional team. The number of professional stakeholders involved in HBPC varies (due to resources, availability etc.). Some services are better funded than others. Reasons can be routines of care, or overemphasizing medical care compared to social care. The number of stakeholders, the variety of disciplines and professional cultures involved, leads to different ways of cooperation in HBPC-teams. HBPC providers are also gatekeepers to other services (such as physiotherapy, intensive nursing, psychosocial support etc.). These providers and agencies (with different (educational) standards and organizational cultures) can also be involved in HBPC.</p> <p>Professionals emphasized the importance of multi-professional cooperation in HBPC. Challenges faced are linked to the need to combine health care, community health care and social care. Community care competence is seen as the base for HBPC but it was also mentioned that professional providers involved in HBPC often do not have the necessary experiences in community care. The main focus is often on physical tasks. The different service approaches (community services, palliative care services) involved in HBPC need to be understood by all professionals involved.</p>

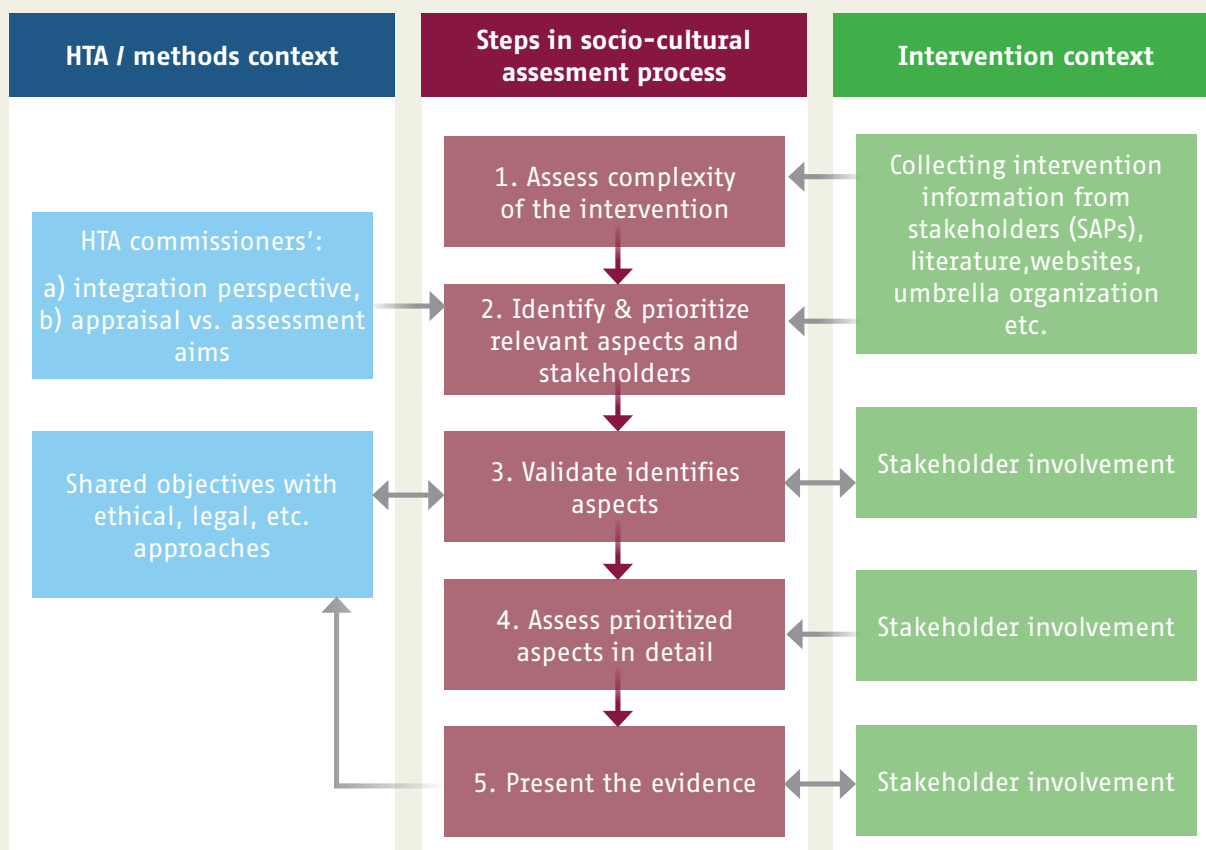
5.3 HOW TO APPLY THE GUIDANCE

The assessment process for socio-cultural aspects of complex interventions in HTA is presented in Figure 11. Column 2 represents the assessment steps of the socio-cultural assessment: 1) the assessment of the complexity of a technology, 2) the identification and prioritization of relevant aspects and stakeholders, 3) the validation of identified aspects, 4) the assessment of the prioritized aspects, and 5) the presentation of the evidence. The assessment is influenced by contextual elements as presented in the first column. That is to say a specific interest of the HTA-agency or of commissioners could for example already emphasize specific aspects as important without conducting a prioritization exercise. Information provided by other parts of the HTA (e.g. the economic analysis, the ethical analyses, etc.) also contextualise the socio-cultural assessment. This means, whenever e.g. moral issues are encountered in the socio-cultural assessment, ethical expertise should be considered and vice versa. As presented in the third column, the context of the technology itself also influences the socio-cultural assessment by offering information on the geographical

background or the specific setting of implementation. This context will also be taken into account in each assessment step. We suggest stakeholder and public involvement to include perspectives of experts familiar with using the technology.

In the following we provide a description of each assessment step, the specific objectives, methods, and results. We show how the presented socio-cultural framework can be applied in each assessment step to identify relevant aspects and stakeholders, to develop research instruments and to structure the presentation of evidence. We further describe how the application of Cultural Theory (see 9.2.4) can help to capture heterogeneity of perspectives. The application of the socio-cultural guidance should include the reflection of implementation, context and patient preferences as described in the INTEGRATE-HTA Model (Wahlster et al., 2016). Whenever possible we provide examples showing interactions between socio-cultural aspects and context, patient preferences and implementation. Whereby patient preferences, context and implementation influence socio-cultural aspects and vice versa (ibid).

Figure 11: Assessment process for the assessment of socio-cultural aspects.



5.3.1 Assessment step 1: Assess the complexity of the intervention

Complex technologies are the main focus in the INTEGRATE-HTA guidance. Knowledge about the different components of complexity could support the identification and prioritization of important socio-cultural aspects and important outcome parameters. Apply the complexity components presented in the chapters 1.2.1 and 4.3.1 - "multiple and changing perspectives", "indeterminate phenomena", "uncertain causality", "unpredictable outcomes", and "history, time and path dependence" to the technology of interest and reflect on their relevance for the socio-cultural assessment by using the socio-cultural framework. The results inform further steps of the assessment process.

Example of the case study on (x)HBPC: The case study on (x)HBPC identified the component "multiple and changing perspectives" as an important complexity component regarding (x)HBPC (see Table 8). By applying the socio-cultural framework we identified its relevance for "the social image of the intervention", "the relationship between users and professionals", and "the relationships between different professional providers" and considered it when reflecting on each of these framework categories in the further assessment steps.

5.3.2 Assessment step 2: Identify and prioritize relevant aspects and stakeholders

Under ideal conditions step 2 includes three sub-steps. These are step 2a – to get an overview of topics and stakeholders, step 2b – to elaborate on identified topics and their prioritization, and step 2c – to ensure heterogeneity of perspectives. Limited resources could require pragmatic adaptations. All the same, the inclusion of different cultural perspectives needs to be ensured.

Assessment step 2a: Get an overview of relevant aspects and stakeholders

Objective: Step 2a aims at obtaining a scope of relevant aspects and stakeholders (including patients and the public). Evidence is collected on a rough level aiming at an overview of aspects. It can be conducted

as part of a broader scoping exercise as indicated in step 1 of the INTEGRATE-HTA Model (Wahlster et al., 2016) which takes a range of assessment aspects into account.

Methods: Depending on the HTA-research question the first step should aim at an overview of aspects, opinions, issues etc. and the identification of stakeholders. At this stage of the assessment it is worth considering a broad range of different sources of information. Screen scientific and non-scientific literature (e.g., journals/ websites of professional umbrella organizations, information from self-help groups etc.), films, published interviews etc. Focus on different opinions, discourses, and the presentation of issues during the screening process.

Following a participatory approach, the involvement of stakeholders as pre-informers is another respectively, an additional option for getting a broad overview. In this case approaches such as the Interactive HTA could possibly work as an overall frame for the assessment (see 5.1.3). Contact a small number of stakeholders (3-4) with a broad scope of the field of interest individually (face-to-face or via telephone) to gather a wide range of information. The structure of the consultations should allow pre-informers to bring in new topics, perspectives, etc. Ask pre-informers to suggest who they think it is important to include in the socio-cultural assessment. In combination with the stakeholders identified in the screening process, this snowball-sampling can improve heterogeneity in perspectives and limit "eminence-based-sampling".

The socio-cultural framework offers a comprehensive set of aspects and related questions to guide the screening process. This can be applied as a kind of checklist structuring the collected information. It also offers a tool to develop suitable interview guidelines for the consultations (see examples in the case study report (Brereton et al. 2016)). If the scoping exercise aims at various assessment aspects, the CICI-framework (Pfadenhauer et al., 2016) could also be an option to quickly address socio-cultural aspects along with various context dimensions such as the geographical or ethical context. In this case the socio-cultural framework should be applied to control whether all relevant aspects have been taken into account. The relevant results need to be fed back into further steps of the socio-cultural assessment, where they will vice versa confirm the relevance of the information gathered in the socio-cultural assessment for other assessment aspects.

Socio-cultural diversity in the sampling structure should be taken into account. Therefore it does not matter if stakeholders will be involved as advisors or as research participants. To ensure a common understanding of the technology, attention should also be given to stakeholders' "understanding of the technology" (a category represented in the socio-cultural framework).

Results: Step 2a ends with a collection of identified socio-cultural aspects related to the technology of interest. Another outcome is a sample of stakeholders to be included in the socio-cultural assessment.

Example of the case study on (x)HBPC: Through pre-informer consultations we became aware of different health service cultures related to a specific care setting (context): clinical health care, community care, and social care. Differences were seen with regard to the professional needs assessments, the foci of care, the status of patient's priorities, relationships between patients and professionals, relationships between professional providers etc. Community health care and social care services are much more experienced in providing care at the patient's home. HBPC-providers should therefore have experience in the field of community care. However, due to their clinical socialization, HBPC-providers often lack familiarity with the patients' home as the place of care provision. Pre-informers advised that representatives (e.g. community nurses, who are not explicitly part of (x) HBPC) should be included in the stakeholder sample.

Assessment step 2b: Elaborate on identified aspects and their prioritization

Objective: To elaborate and prioritize the aspects identified in step 2a.

Methods: To elaborate on and to prioritise the aspects identified in step 2a the participatory approach can be applied. Participation can be done differently (e.g., sending a questionnaire, personal interviews, or telephone interviews). However, research shows that face-to-face involvement improves the satisfaction of participants (Gagnon et al., 2011). Therefore we suggest personal interviews/ consultations. Pre-informers can also be involved at this stage.

Structure the interviews again using the socio-cultural framework, but give priority to additional aspects introduced by stakeholders. Write down socio-cultural aspects addressed by pre-informers on cards and present them to the interviewees. This ensures an intensive

and critical analysis of the mentioned aspects and offers space to develop different perspectives and scenarios. Asking stakeholders to describe a typical/ critical situation could encourage reflection, thereby helping to capture cultural and political differences and controversies. The application of the four cultural types (see 9.2.3 and 9.2.4) can help capturing heterogeneous cultural perspectives.

The prioritization of aspects by individual stakeholders completes this assessment step. Examples for prioritization approaches are presented e.g. by Janssen et al. (2014) or Ryan et al. (2001). To improve the understanding of related background theories, ask stakeholders to give reasons for their judgements. Cluster the prioritized aspects by using the socio-cultural framework to reduce the number of issues without losing the information.

Results: Step 2b results in an elaborated and prioritized list of socio-cultural aspects relevant for the assessment of the health technology from the perspective of individual stakeholders.

Assessment step 2c: Conduct group consultations to ensure heterogeneous perspectives

Objective: The aim of step 2c is to capture various perspectives of each stakeholder group.

Methods: Regarding prioritization HTA-agencies face the problem of changing priorities. According to Abelson et al. (2003) individual prioritizations change when the opportunity for discussion is given. Therefore group consultations with stakeholders who have different perspectives on the aspects identified in step 2b are of advantage. Share the results of step 2b anonymously before the meeting and introduce them during the discussion. This anonymous introduction of different perspectives (not referring to a specific person) can support a critical discussion and help avoid difficult group dynamics.

Summarise the socio-cultural aspects during the group meeting e.g. using moderation cards. Ask participants for missing aspects and add them. A prioritization of all presented aspects by the group completes the assessment step (for details on prioritization methods see (e.g., Janssen et al., 2014; Ryan et al., 2001). Reasons for the stakeholder's prioritization should be ascertained and noted.

Step 2c can replace 2b. This will however reduce the information given especially with regard to controversial aspects. Here group dynamics could complicate the detection of diverse perspectives as well as of differing priorities. The socio-cultural framework is applied to

structure the discussion and to analyse the collected information.

Results: An elaborated and prioritized list of socio-cultural aspects relevant for the HTA can be presented at this stage of the assessment. It helps to ensure that HTA-questions with practical relevance are posed and prevents of asking the wrong research questions and solving the wrong problem (Mitroff & Featheringham, 1974).

Example of the case study on (x)HBPC: We conducted a group discussion with patients and relatives receiving (x)HBPC for step 2c. The discussion was guided by the socio-cultural aspects identified in the foregoing steps, which were structured by the socio-cultural framework (see the case study report (Brereton et al., 2016) for further information). Stakeholders added “the insecure continuity of care” in (x)HBPC as an additional aspect of relevance. All aspects were ranked by the stakeholders, each of whom had 10 points and could distribute them among all aspects. After organizing the aspects in the socio-cultural framework the category “user-professional-relationship and decision-making” was identified as the most important for this group. This corresponds with the aspect identified through the complexity assessment in step 1.

5.3.3 Assessment step 3: Validate the identified aspects

Objective: The aim of this step is to validate the prioritized aspects.

Methods: Present the elaborated and prioritized list of socio-cultural aspects to the stakeholders again, individually. This can be done face-to-face, by telephone or email). The description should be structured in a systematic and comprehensive manner, e.g. according to the socio-cultural framework. Consultants will be shown their own individual prioritization (step 2b) and that of the group they belonged to. They are then requested to prioritize the aspects again and to give reasons for their choices. Making the reasons for choices transparent could help to understand how decisions are made and to understand potential changes.

Results: Differences in prioritization preferences between stakeholders and stakeholder groups as well as their changes become transparent and can be reflected on. Depending on the research question and the purpose of the HTA aspects identified as being most important or as the most controversial can be evaluated in more detail.

5.3.4 Assessment step 4: Assess prioritized aspects in more detail

Objective: Step 4 offers options to assess specific aspects in more detail emphasizing heterogeneity of perspectives.

Methods: There are several options. If the evidence base is available, a literature review can be conducted. The socio-cultural framework can structure the evidence collection and analysis. However, it could be difficult to identify cultural differences.

It is also possible to conduct another stakeholder group meeting including representatives of heterogeneous stakeholder groups, who elaborate on the specific aspects. The socio-cultural framework offers a tool to structure the discussion and can be used to develop a question list. In addition the cultural specific description of each category (see 9.2.4) can help stakeholders to reflect on cultural heterogeneity. If you present the cultural types associated with the specific socio-cultural aspect you probably decrease social desirability (linked to the labels “hierarchists”, “fatalists” etc.) by labelling the types as A, B, C, and D.

If the evidence base is low and the resources are available primary research can also be conducted. The position of the participants as research partners (not consultants) can require ethical considerations. The socio-cultural framework can inform the development of research instruments such as questionnaires or interview guidelines.

In any case, additional aspects identified in the previous steps should be reflected on as interacting variables (e.g. context or conditions) related to the prioritized aspects.

Results: Step 4 results in a detailed assessment of the aspects/ framework category prioritized in steps 2 and 3. Relationships to other framework categories should be taken into account. Heterogeneous perspectives are captured and described.

Example of the case study on (x)HBPC: In the case study on (x)HBPC, a participatory approach was chosen for steps 2 to 4. Due to organizational conditions linked to the case study, we used the group of professional stakeholders (only) to evaluate the prioritized aspect “user-professional-relationships and decision-making”. Stakeholders applied the cultural types related to the “user-professional-relationship and decision making” (see 9.2.4) during their discussions. Reflecting on the relationship between patients and professionals in (x)HBPC using the cultural types, the professional providers became for example aware of challenges related to their

idea of patient-centeredness, which is understood as autonomy for patients. Through applying the cultural types they became aware that patient-centeredness could also mean to fulfil a patient's request for professional authority (patient preferences). However that would challenge professionals' egalitarian understanding of providing palliative care, which emphasizes an equal relationship with patients on an eye level and declines professional authority. This idea of providing (x)HBPC could also be challenged by hierarchical setting of a nursing home (context). In this case (x)HBPC is implemented in hierarchical structures which could contradict to a democratic decision making and shared responsibility. As well it could be more difficult to address relatives and their needs.

5.3.5 Assessment step 5: Present the evidence

Objective: The final step 5 aims at combining and presenting the results of all previous assessment steps.

Methods: The socio-cultural framework offers a structure for the presentation of evidence. Repeat the information relevant for different framework categories and explain the relevance for each category. Reflect on relations between different categories as well as on different levels of social organization (micro-, meso-, macro-level). Make overlaps with other assessment parts (e.g., the assessment of ethical aspects or of patient preferences) explicit and feed-back the information. Overlaps with results identified by using different methods could improve validity and soundness of the results identified in the socio-cultural assessment.

Results: A comprehensive list of evaluated socio-cultural aspects framed by the socio-cultural framework.

5.4 CONCLUSION

5.4.1 Main insights

The guidance consists of two parts: 1) The framework to identify, structure, and assess socio-cultural aspects in HTA (see Figure 10) and 2) the five steps assessment process (see Figure 11). The framework can be applied to each of the assessment steps. The assessment process and the socio-cultural framework, both facilitate

- ▶ the identification and prioritization of important socio-cultural aspects/ discourses as well as heterogeneous perspectives related to a health technology,

- ▶ the identification and involvement of heterogeneous stakeholders,
- ▶ the determination of research agendas on socio-cultural aspects, and
- ▶ the assessment of socio-cultural aspects linked to a particular technology in a culturally sensitive way.

The guidance also provides an overview of methods that can be used to address socio-cultural aspects in HTA.

5.4.2 Strengths and limitations of the current method

The assessment approaches make it possible to identify and assess a variety of socio-cultural aspects related to a health technology to be captured. Apart from the presented assessment methods the guidance offers a structure for the assessment of complex technologies and allows for flexibility. The latter is of special importance in complex technologies, which do not allow for a one-size-fits-all approach.

The application of theoretical approaches from the field of social and cultural sciences enables the capturing of heterogeneity of perspectives. Cultural Theory is used as an example to reflect the framework categories from different cultural perspectives (see 9.2.4). However, the application of this part of the guidance will require experience in the field of analysing socio-cultural aspects.

The guidance offers an instrument to identify and elaborate on socio-cultural aspects relevant for a health technology. Interrelations between the framework categories are mentioned and described in the assessment. However, the analysis of mutual interactions and feed-back loops needs to be further developed.

Although socio-cultural aspects are part of most HTA-definitions, in practice they are rarely addressed. While this guidance has been developed with a focus on complex technologies it can be applied to any health technology.

5.4.3 Outlook

We hope that the guidance on socio-cultural aspects will be used in the HTA-practice and be continuously improved upon. It has the potential to demonstrate the high importance of socio-cultural aspects, from the understanding of a technology and the addressed health issue, to socio-cultural aspects of its implementation and organization. To ensure improvement, we would greatly appreciate feedback from readers, users and the interested public.

6 GUIDANCE TO ASSESS LEGAL ASPECTS

By: Jan Brönneke, Bjørn M. Hofmann, Kristin Bakke Lysdahl, Gert Jan van der Wilt, Benedikt Buchner

6.1 INTRODUCTION

6.1.1 Purpose and scope of the guidance

The aim of this guidance is to provide a framework to allow those conducting an HTA without profound legal education to identify legal aspects relevant for the assessment of complex technologies and, consequently, to allow for a better integration of legal aspects in HTA of such technologies.

6.1.2 Background

Legal aspects, although acknowledged as components of HTA (Potter et al., 2008), are often neglected in HTA reports (Mossialos et al., 2004). Research shows that legal aspects have either been discussed with regard to a certain technology or medical situation (for example Prenatal/Preconceptional and Newborn Screening (Potter et al., 2009), Genomics and Cancer research (Ellerin et al., 2005)) or concerning only a limited area of legal questions (such as European IT-Law (Mossialos et al., 2004)). Papers on (methods for) the integration of ethical, legal and social issues (EL-SIs) in HTA mostly concentrate on ethical and social issues while only briefly dealing with legal questions (see for example Braunack-Mayer & Palmer, 2008).

Reasons for this lack of integration of legal aspects in HTA (and especially in the assessment of complex technologies) seem to be manifold: the applicable legal rules differ extremely, depending on the technology/intervention in question. For example, legal questions in assessing a new medical device like an X-ray generator mainly refer to regulations like patent-law or safety- and liability-regulations, while in the assessment of a psycho-social intervention the right of self-determination might be of higher importance. This also applies to complex technologies (such as palliative care interventions) that are often regulated by a more diverse set of legal norms than less complex technologies (e.g. cardiac stents or treatment with drugs). Particularly the rights of the patient are often affected more by complex technologies. These kinds

of technologies are, among others, characterised by a higher number of single, interwoven interventions, including surgical, physical, psychological interventions as well as drug use than (single) non-complex technologies (see Chapter 1.2.1). An example is palliative care in which most legal norms aim to protect the patient's rights (especially the rights to autonomy and privacy). These norms are based on the assumption that the patient is exceptionally vulnerable in the condition of suffering from a progressive illness without expectations of getting cured and with a limited life expectancy. Issues of authorisation and financing the application of complex technologies also involve far more legal norms than less complex technologies. Perhaps the most serious challenge to assess legal aspects in HTA with the help of a generic approach concerns international applicability of such an approach: Although transnational (especially norms of professional responsibility e.g. Declaration of Helsinki, Declaration of Geneva), international (e.g. Universal Declaration of Human Rights/UDHR, International Covenant on Economic, Social and Cultural Rights/ICESCR) or supranational (e.g. The European Social Charter) norms do have an influence on the development and use of health technologies, it is very limited in comparison to national legislation.

These circumstances pose a challenge for developing a generic structured approach for identifying and analysing relevant legal questions and respective norms within the HTA-process. For this reason, some authors propose to consider legal aspects in the stage of decision making, rather than integrating them in the assessment itself (Potter et al., 2008). However, integrating legal aspects into the HTA-process is likely to increase the relevance of HTA-findings for policy and practice (Battista & Hodge, 1999; Lehoux et al., 2004). Thus the development of such a structured approach can be seen as crucial to the benefit and impact of HTA.

6.1.3 Existing approaches to address legal aspects in HTA

The assessment of legal aspects seems to be best developed regarding the evaluation of genetic testing: some of the existing frameworks explicitly refer to legal questions of interest for that particular technology (Potter et al., 2008). However, the legal questions to be addressed as well as the method of assessing them differ considerably. These include merely pointing out that legal questions have to be considered (Kroeseet et al., 2007), considering legal aspects across all other

domains (Goel, 2001), raising specific questions regarding consent, ownership of data and/or samples, patents, licensing, proprietary testing, obligation to disclose, or reporting requirements²⁸ and incorporation of 'legitimacy' when assessing clinical utility (Burke & Zimmern, 2007).

The few existing "generic" (i.e. not specified for a certain technology) approaches reflect the problems identified above. One approach to consider legal aspects is (the legal domain of) the EUnetHTA HTA Core Model, which is a generic approach, i.e. not specifically designed for the assessment of a specific technology. The EUnetHTA HTA Core Model highlights the most important legal aspects regarding health technologies, which can be summarised as follows:

- ▶ Issues related to health care policy at the local, national or international level, such as equality in and distribution of health services or reimbursement regulation;
- ▶ Issues related directly to the technology in question such as proper authorisation, patent/license issues, product safety, guarantee and liability issues;
- ▶ Issues directly related to the patient and his/her basic rights and freedoms, such as issues of autonomy, informed consent, privacy and confidentiality as well as his/her safety;
- ▶ Issues related to health care professionals rights and duties (in parts corresponding to patient's rights);
- ▶ Legal regulation of novel/experimental techniques.

The HTA Core Model furthermore distinguishes between medical/surgical interventions, pharmaceuticals, diagnostic technologies and screening technologies for each of which the Core Model slightly differs.²⁹

Based on the EUnetHTA HTA Core Model, Engelke & Droste developed a framework which, besides considering the Core Model differentiation, also distinguishes between legal aspects regarding general medical specifications of the technology (e.g. for which medical indication(s) the technology shall be used and whether this is covered by the relevant national health care system) and the legal framework of applying the technology (Engelke & Droste, 2014). This implies asking questions about, for example, legal liability, professional standards, reimbursement etc. Moreover the work of Engelke & Droste contains a structured approach for conduc-

ting searches on legal aspects, identifying the most important actors, databases and other sources of information as well as a practice-based guidance on structuring the research process. In the guidance Engelke & Droste propose to first categorize legal aspects based on three questions: what kind of technology is subject of the assessment (e.g. is it a drug, a medical device or a diagnostic test?), which medical or non-medical field is relevant (e.g. genetics, transplantation-medicine, palliative care?) and who are the addressees of the technology are (e.g. ill patients or people in good health, how is their state of mind, are they able to make decisions or are they unconscious?). In the second step it is proposed to identify the relevant sources of legal regulations (transnational, national, international, EU-wide regulations) and the legal relations between the involved actors (civil contracts, public obligations). In a third and fourth step the specific relevant legal norms and court decisions have to be identified and analysed. This approach is very helpful in structuring the assessment of legal aspects and is used as a basis for the approach described in this guidance.

The approach of Engelke & Droste is advanced with regard to the specific legal methodology: The legal method, in science as well as in practice, is the method of hermeneutics: the starting point of (nearly) every legal argument is an existing or potentially existing legal norm. Such a norm can have various sources such as a parliamentary act, a court decision or the peremptory norms of *ius cogens* or customary international law. That said, the first and second step in the assessment of legal aspects is to acknowledge whether the technology in question, and more specifically the use of this technology does have legally relevant effects, and what these effects might be. Based on the identification of possible legal aspects the relevant legal area (for example private or public law, criminal law, or international law) can be identified in a third step. The approach of Engelke & Droste, although generic in the sense of being applicable to different technologies, is based on the German legal system. This means that it is only partially applicable in other legal regimes, such as – for example – the common law in which court decisions play a more important role than in civil law-regimes.

The newest elaboration on a generic framework to identify legal aspects in HTA is the one by Widrig &

²⁸ ACCE Model List of 44 Targeted Questions Aimed at a Comprehensive Review of Genetic Testing, http://www.cdc.gov/genomics/gtesting/ACCE/acce_proj.htm (11/02/14).

²⁹ However, this differentiation seems to be not precise enough and is therefore not made in this paper.

Tag (Widrig & Tag, 2014). This approach includes not only the legal implications of the assessed technology (called “Inside Perspective” and “Micro level” by Widrig & Tag) but also the legal regulations on HTA itself (called “Outside Perspective” and “Macro level”). However, as this guidance is on the assessed technology as subject to regulation rather than the regulation on HTA itself, the framework on the “Outside Perspective” is not further elaborated here. Regarding the “Inside Perspective”, Widrig & Tag have identified five legal areas of relevance. These are legal norms concerning the patient, the care provider, the technology itself, financing the use of the technology, and finally norms regulating the methodology of the assessment (e.g. use of certain clinical endpoints, trials etc.). Widrig & Tag elaborate further on these issues, however, the specific application of the framework – especially for scholars with a non-legal background – remains rather unclear.

6.2 GUIDANCE DEVELOPMENT

This guidance is based on the approaches mentioned in (Chapter 6.1.3) (Engelke & Droste, 2014; Widrig & Tag, 2014; the HTA Core Model from EUnetHTA). The problem of international applicability of a structured method to integrate legal aspects in HTA was taken into account by identifying nine core issues, which are relevant in every European legal system.

The guidance has been applied in a case study on home-based palliative care with and without reinforced caregiver support in UK. The results of the case study indicated difficulties in the application of the guidance by HTA experts respectively palliative care experts with no legal background. Based on this outcome the guidance was revised carefully especially with respect to clearer step-by-step explanations (see 6.3.1).

6.3 APPLICATION OF GUIDANCE ON IDENTIFICATION OF LEGAL ASPECTS IN HTA

Every health technology has legal implications, i.e. affects legal aspects. This guidance provides a set of questions and corresponding explanations to guide identification of nine potentially affected legal aspects³⁰. These core legal aspects might require con-

sideration within the HTA process. A generic guidance like this one can

The legal aspects of general importance are:

1. Autonomy of the Patient I: Informed Consent
2. Autonomy of the Patient II: Alternative Forms of Consent
3. Autonomy of the Patient III: Privacy and Data Protection
4. Market Authorisation I: Medical Devices
5. Market Authorisation II: Medicinal Products
6. Clinical Trials
7. Intellectual Properties
8. Reimbursement in Public Health Care Systems
9. Special Medical Fields

Due to the wide variety of legal norms as well as of the technologies, and especially due to the case-related approach of legal practice and science, this generic guidance cannot address every potentially affected legal aspect and cannot be used to answer specific legal questions that may arise when applying the technology, to decide on whether the technology faces insurmountable legal obstacles, or especially to weigh the gravity of legal aspects and with that to determine whether one technology is legally ‘preferable’ to another technology. These can only be done by an in-depth analysis of the specific case, i.e. the specific technology with regard to the specific legal question.

Therefore this guidance cannot substitute professional legal advice! When in doubt, seeking the advice of a legal expert should always be considered. Using this guidance can help to decide on whether expert advice is necessary.

The identification of potentially relevant legal aspects involves two steps: the determination of the relevant decision level (micro, meso or macro, (see 6.3.1) for preselection of issues and the actual identification of issues. A third step is the decision on whether to assess identified issues further and to relate this assessment to other parts of the HTA. Figure 12 shows how decision level, specific issues and relations to other parts of the HTA are connected. The issues and their relations to other aspects of HTA is explained in (chapter 6.3.4, Nine Core Issues).

³⁰ These issues have been identified on the basis of the few existing sources on legal aspects (see above).

6.3.1 Determining relevant decision level (Step 1)

To use this guidance, firstly the level of the relevant decision has to be determined. This guidance distinguishes between three of such levels:

1. Decisions on the micro level concern the relationship between health-care professionals and patients. Relevant decision makers (that also means: target groups of the HTA) are mostly doctors and patients.
2. Decisions on the meso level concern choices of health care organisations. Relevant decision makers/target groups of the HTA are mostly hospitals, or other organisations that provide health care services.

3. Decisions on the macro level concern politics and administrative choices. Relevant decision makers/target groups of the HTA are mostly legislative and administrative bodies as well as institutions that are legally assigned to decide on fundamental national health care politics and policies (such as the Joint Federal Committee, G-BA in Germany or the NICE in UK).

Determining the level of decision helps in pre-selecting relevant issues: as illustrated by the "Decision level" column in Figure 12, some issues are of higher relevance on the micro and meso level while others are higher relevance on the meso and macro level. Determining the relevant level of decision-making will therefore help you to focus on the important legal aspects rather than trying to assess aspects that have no relevance in the context of that

Figure 12: Localisation of Legal Aspects in HTA.

Decision level	Legal issues	Overlapping HTA aspects
Micro and Meso Level	1. Informed Consent	Ethical and Socio-Cultural Issues
	2. Alternative forms of Consent	
	3. Privacy and Data Protection	
Meso and Macro Level	4. Authorisation of Medical Devices	Clinical Issues and (possibly) Ethical Issues
	5. Authorisation of Medicinal Products	
	6. Clinical Trials	
	7. Intellectual Property	Legal and Ethical Issues
	8. Reimbursement in Public Health Care Systems	All parts of the HTA
	9. Special Medical Fields	Ethical and Socio-Cultural Issues

specific HTA. The question of the relevant decision level is often of relevance for the complete HTA and therefore addressed in the general scoping exercise (please, see step 1 of the INTEGRATE-HTA Model (Wahlster et al., 2016) for further information on scoping exercise). The results of that exercise can be used here.

6.3.2 Determining specific relevant legal aspects (Step 2)

In a second step, the following sections (6.3.4), containing the explanation of each of the nine aspects. It can be used to evaluate the importance of every issue for the specific assessed technology. Each section starts with an initial question (A.), which helps clarifying whether the issue is of importance, or not. If the answer to a question is affirmative, the legal issue is affected by the technology. Following to the initial question, the legal issue is explained roughly to create an understanding of whether further consideration of the issue within the HTA is required (B.). After that, each section contains a short overview on legal sources for that specific issue, especially whether the issue is mainly regulated by national law or rather by EU-wide regulations (C.). This part can be used if the primary legal sources shall be evaluated in order to get a more profound understanding of the issue.³¹ If further assessment of the issue is considered within the HTA, the following part (D.) points out the relations of the legal issue with other, also non-legal aspects. The information given here can be used as an indication to the localisation of the assessment within the HTA-process. Each section closes with an explanation of which decision level the issue is of higher importance (see above, Step 1.) as well as hint on whether professional legal advice should be considered (E.).

Correspondingly each of the following sections on a specific legal issue comprises:

- A. The initial question,
- B. Explanation of the legal issue, including examples where applicable,
- C. Legal sources relevant for the affected legal aspects,
- D. Relations to other parts of the HTA,
- E. Reference on relevant decision level as well as on the necessity of professional legal advice.

6.3.3 In-depth assessment of identified aspects (Step 3)

Exercising the guidance helps to identify the most relevant legal aspects. Whether or not a rigorous assessment of the identified issue has to be conducted can only be decided on within the specific case and can therefore not be answered by this guidance. However, reading the guidance thoroughly and understanding the legal rationale of the norms regulating the identified issues should enable the HTA-conductor (or the addressed decision maker) to either dismiss further legal assessment or to further assess and to adapt the technology itself or the usage of the technology accordingly if required. If a further assessment of legal aspects is planned, it can be tied to the assessment of those issues identified in step 2 as overlapping or related parts (lit. D. of each section).

6.3.4 Nine Core Issues

Aspect 1: Autonomy of the Intervention Recipient I – Informed Consent

Autonomy is of core relevance in law, especially in private law, which regulates the relationships of private entities among each other. This also includes the relationships of patients to their doctors or other health care service providers. Autonomy of the patient is therefore often an issue when decisions on specific treatments have to be made by doctors and patients. This is especially the case if the following question can be answered in the affirmative.

- A. Question: Is the technology an intervention that is used in direct physical or psychological contact with the patient?
- B. Explanations: Direct physical or psychological interventions interfere with the physical or mental integrity of the patient. Examples are the surgical appendectomy or the intravenous injection of a saline solution but also less clearly interfering interventions such as exposure therapy for anxiety disorders or talking therapy in psychoanalysis. Some health technologies might not interfere with the physical or mental integrity of the patient even though they have a medical and therapeutic effect. An example might be the use of a certain patient management software or the implementation of a certain clinical pathway as an organisational measure.

³¹ Regarding those issues subject to Europe-wide regulation, further explanation of the legal sources and background can be found in Legal Appendix I.

The autonomy of the patient is protected by different legal norms concerning the informed consent: The patient has to consent to every therapeutic step that is intervening with his physical or mental integrity and has to do so with full knowledge about all necessary information on the intervention. Failure to inform the patient and giving him/her the opportunity to decide autonomously can constitute a personal injury and with that a criminal offense.

C. Legal Sources: Informed consent is mainly regulated by national norms. The obligation to provide the patient with all information necessary to consent normally lies with the doctor. The doctor-patient-relationship can be regulated by private law in systems in which doctors are working on their own behalf (e.g. §§ 630a seqq. Of the German Civil Code 'Bürgerliches Gesetzbuch') or by public law in systems in which doctors are employed by the public health care service (e.g. in Great Britain). Use of an intervention without the patient's informed consent can constitute a criminal offence. Criminal legislation is mostly done on the national level (penal codes)

D. Relations to other parts of the HTA: The legal issue of informed consent is dependent on other legal aspects, especially the legal issue of authorisation of medicinal products and medical devices (Aspect 4) as well as the legal issue of reimbursement (Aspect 8). These limit the patient's choices as a non-authorised technology can under no circumstances be used on the patient, while a technology that is not reimbursed by the public health care system could be unaffordable for the patient.

Example: In a system that does not allow the use of a certain pain-relieving but at the same time highly life-shortening drug in palliative care by denying authorisation (e.g. on the grounds of patient's safety), the patient's choice is limited to other, authorised drugs.

Moreover the basic idea of informed consent is also strongly shaped by ethical and socio-cultural norms as these norms influence the definition of the protected private sphere.

E. Relevant decision level and necessity of legal advice: Although the issue of autonomy of the patient is of paramount importance for the use of a technology (not least because of the severe legal consequences of failure to obtain informed consent) its importance for HTA is often limited. As the obligations to safeguard the patient's autonomy lies with the treating doctor, only HTAs directly affecting the organisational relationship between doctor and patient have to include

the issue prominently. Assessments on questions of the systems level therefore can often neglect the issue.

Example: The question whether a reinforced home based palliative care-service is being paid for by the public health care system does not affect the question when and by whom the informed consent of the patient has to be obtained. Therefore an HTA on such a reimbursement question can mostly forgo that question. On the other hand an HTA on the question how to provide such a service by a specific provider in a specific setting has to consider the issue prominently to guarantee that nurses or are other employees of the service are aware of their duty to obtain the patient's informed consent.

As the consequences of failure to comply with rules concerning the autonomy of the patient can easily be very severe for those who use the health technology (as it might result in high damage claims of the patient), a legal counsel should be consulted in case that this aspect is assessed in depths.

Aspect 2: Autonomy of the Intervention Recipient II – Alternative forms of Consent

A. Question: Is the future patient potentially not of age of majority or does not have the capacity to consent legally binding out of other reasons?

B. Explanations: Every intervening treatment (see Aspect 1) needs the informed consent of the patient. In most countries consent needs to be an implicit or explicit declaration of a person of full age. In case that the technology shall be used on children or patients that are not capable of consenting for example because of disability or unconsciousness. This is most always the case with technologies specifically designed for paediatrics and can also apply to technologies used in palliative care.

In case that the informed consent cannot be obtained directly from the patient, other ways of legitimisation have to be found. Informed consent can be substituted by valid pre-emptive consent through legally valid advance health care directive or right to child custody (for example of parents). If alternative legitimisation is available at all or not feasible to obtain before treatment (e.g. in emergency cases), the presumed will of the patient has to be assessed by the responsible doctor considering rules of professional responsibility.

C. Legal sources: Advance health care directive and right to custody are regulated on the national level by private law. Rules of professional responsibility

are mostly laid down in guidelines of international conferences and organisations (such as the Helsinki Declaration of the World Medical Association) or of national organisations (for example standards of good medical practice of the General Medical Council, UK) that mostly implement and specify the more general international rules. Whether these norms legally bind doctors directly, depends on corresponding legal norms for example criminal law applied on medical malpractice.

Example: The fundamental principles on aid for the dying of the German Bundesärztekammer lays down professional ethical rules concerning the consent of incompetent or incapacitated dying patients. These rules, besides others, are used by criminal courts to determine the appropriate medical standard in malpractice cases and therefore have to be considered by the doctors to prevent being held liable for malpractice.

- D.** Relations to other parts of the HTA: If no alternative form of legitimisation is available, professional responsibility rules build the framework for the decision of the doctor. These rules can be norms of medical ethics rather than legal and legally directly binding norms. Therefore the assessment of this issue can often be conducted parallel to the assessment of ethical norms.
- E.** Relevant decision level and necessity of legal advice: See Autonomy of the Intervention Recipient I – Informed Consent.

Aspect 3: Autonomy of the Intervention Recipient III – Privacy and Data Protection

- A.** Question: Does the use of the specific technology involve the collection and processing of patient's data?
- B.** Explanations: Medical treatment is based on data about the patient used for anamnesis, diagnosis and indication. These data include for example the name, address, illness, medical history of the patient etc. In complex technologies often a number of different users of the technology (e.g. doctors, nurses) are involved, between which these data are forwarded (i.e. 'processed').

Information privacy is part of the autonomy of the patient and becomes more and more important as technological progress makes the fast and extensive transfer and use of data possible and often necessary. Laws on information privacy basically grant patients the right to know which data is collected of them and for which purposes as well as to determine every data collection

and processing themselves. Collection and processing of patient's data therefore requires the informed consent from the patient for every specific purpose.

- C.** Legal sources: Privacy and data protection is strongly regulated by European Union law, specifically the Data Protection Directive 95/46/EC. This directive (as every EU directive) obliges the state to implement appropriate rules in national law to achieve the object of the directive, which means according national norms exist in every Member State. These national norms are the prior sources for the assessment of the issue, however the EU directive is of paramount importance for the interpretation of the national norms. For further explanation about EU wide regulation of information privacy, see Chapter 9.3.
- D.** Relations to other parts of the HTA: As the protected private sphere of patient's autonomy is (among others) defined by ethical and socio-cultural aspects (see Aspect 1), Intervention Recipient I – Informed Consent], the idea of privacy is strongly connected to these aspects, too.

Example: Questions on appropriate behaviour of nurses who, on delivering home-based palliative care, enter the patient's household, are (among others) shaped by (in parts professional) ethics and social norms.

- E.** Relevant decision level and necessity of legal advice: See Autonomy of the Patient I – Informed Consent.

Aspect 4: Market Authorisation I – Medical Devices

Many medical devices as well as medicinal products (pharmaceutical drugs) need to be authorised by a competent body before introduction to the European Market. Without authorisation, the trade and use of such products is prohibited by law. Therefore market authorisation can be a *conditio sine qua non* and failure to obtain authorisation an absolute hurdle for the use of the technology.

- A.** Question: Does the technology comprise a medical device?
- B.** Explanations: Medical devices are any instruments, apparatuses, appliances, software, materials or other articles, intended by the manufacturer for diagnostic and/or therapeutic purposes for human beings and take effect physically, mechanically and/or physicochemically. These include for example injection needles, blood bags, wheelchairs, rinse-solutions, defibrillators, condoms, wound drainage products, surgical suture, cardiac pacemaker, cochlear implants, In vitro diagnostics and many more. Differentiating

between medical devices and cosmetic and lifestyle products as well as pharmaceutical drugs can be problematic in borderline cases.

Medical devices have to be authorised by a competent body before they can get introduced to the European market. Marketing, trade and use of non-authorised medical devices can cause considerable legal and public liabilities and can even constitute a crime punished under national criminal law. Therefore the appropriate authorisation of a medical device has to be ascertained before using the technology. This can be done by checking whether the device in question is labelled with the 'CE marking'. The marking proves the conformity of the devices technical specifications with the standards for authorisation. These standards and the according procedures for technical review depend on the potential risk that the medical device is putting on the patient and are reflected in four different classes of medical products: class I for devices with the lowest risk, IIa and IIb for medium and increased medium risk and class III for devices with a high risk for the patient. Invasive devices for example have to meet higher standards than such devices that are used externally, perhaps even without any contact with the patient.

Example: Cochlear implants are active implantable devices that fall within the category of devices with the highest possible risk for the patient class III (as all active implantable devices). The review process comprises the strictest procedures provided by the law (for example complete quality management-system) that also require inspection by an external notified body. On the other hand medical apps for organisational use in a hospital fall within class I as they do not pose any danger on the patient. That means the producer can place the CE marking on the product himself without inspection by a notified body.

Besides the technical standards a medical device has to meet to be eligible for authorisation it also has to fulfil clinical requirements, including a positive benefit/risk ratio. The clinical net benefit has to be proven by a clinical evaluation, either based on existing clinical data on equal devices or on a clinical investigation, the latter being mandatory for nearly all class III devices and implantable devices. More specific rules on the clinical evaluation can be found in national laws or directives, such as the German directive on clinical evaluation of medical products (Verordnung über klinische Prüfungen von Medizinprodukten).

Authorisation of medical devices is fully harmonised by the European Union. The central legal sources are the Medical devices directive 93/42/EWG, the in vitro diag-

nostics medical devices directive 98/79/EG, and the active implantable medical devices directive 90/385/EWG. These directives completely determine the classes, the according procedures for technical reviews as well as the notification of the notified bodies and oblige the Member States to enact national laws accordingly. These national laws follow the directives in detail and differ only insignificantly. For further explanation about EU wide regulation of the authorisation of medical devices, see Chapter 9.3.

C. Legal sources: Authorisation of medical devices is fully harmonised by the European Union. The central legal sources are the Medical devices directive 93/42/EWG, the In vitro diagnostics medical devices directive 98/79/EG, and the Active implantable medical devices directive 90/385/EWG. These directives completely determine the classes, the according procedures for technical reviews as well as the notification of the notified bodies and oblige the Member States to enact national laws accordingly. These national laws follow the directives in detail and differ only insignificantly. For further explanation about EU wide regulation of the authorisation of medical devices, see Chapter 9.3.

D. Relations to other parts of the HTA: As an evaluation of the clinical effectiveness and safety is required for the authorisation of a medical device, the assessment of this legal aspect is tightly connected with the assessment of clinical aspects. This is especially the case if a clinical investigation has to be conducted. In this case, results of the assessment of ethical issues can be used, as ethical standards for clinical trials (such as the Helsinki Declaration) have to be considered in the investigation. For further information on legal regulations of clinical trials, see Aspect 6.

E. Relevant decision level and necessity of legal advice: A detailed assessment of the authorisation of a medical device is not necessary if the device is already authorised (labelled with the CE marking). However, if the technology comprises a new medical device or an old medical device with a substantially new scope of application (for example a bicycle ergometer for physical training after implantation of hip joint replacements that shall then be used for diagnosis coronary heart diseases) authorisation of the medical device is of paramount importance. In these cases a legal counsel or a legally trained engineer for medical devices should be consulted.

Aspect 5: Market authorisation II – Medicinal Products

A. Question: Does the technology comprise a medicinal product?

- B. Explanations:** Medicinal products are all kind of pharmaceutical drugs that are subject to admission. Medicinal products take effect by pharmacological, immunological, or metabolic reaction. There are borderline cases in which the differentiation especially from medical devices and cosmetic products can be difficult.

Example: Swelling agents as medical diet products to lose weight can be seen as medicinal products because they physically fill the stomach and with that prevent the patient from becoming hungry. On the other hand they can be seen as pharmaceutical drugs as they slow down the metabolism by replacing metabolizable food.

Medicinal products have to be authorised before they can be introduced to and used in the European market. Marketing, trade and use of non-authorised medicinal products can cause considerable legal and public liabilities and can even constitute a crime punished under national criminal law. Authorisation can be granted by a national competent body as well as by the European Medicines Agency and is based on the pharmaceutical quality, clinical safety and efficacy of the product. These have to be proven by physico-chemical, biological or microbiological tests, toxicological and pharmacological tests, and clinical trials, which have to be provided in the so-called Common Technical Document by the producer. If the assessed technology comprises the use of a medicinal it has to be ascertained that the drug is authorised by checking the national and EU-wide registers of the competent bodies.

- C. Legal sources:** Authorisation of medicinal products is exhaustively regulated by the European Union. Central legal sources are the directive 2001/83/EC on the Community code relating medicinal products for human use as well as the regulation (EC) 726/2004 on the Community procedures for the authorisation and supervision of medicinal products for human use and the European Medicines Agency. National laws and directives have been established according to the European requirements. These are primarily important for authorisation by the national competent authority and do not differ substantially from the EU provisions. For further explanation about EU wide regulation of the authorisation of medical products, see Chapter 9.3.

- D. Relations to other parts of the HTA:** Central to the authorisation of medicinal products is the proof of their clinical safety and effectiveness, the assessment of this legal issue is therefore strongly connected with the clinical assessment of the technology in question. This connection is two-sided: The results of the clinical assessment in an HTA can be used as sources for

the authorisation process as well as the resources and results of the authorisation can be used for further clinical assessments in an HTA. In the first case, the standards for authorisation set out by the law have to be assessed before starting the clinical assessment to plan the latter one accordingly.

- E. Relevant decision level and necessity of legal advice:** A detailed assessment of the authorisation of a medicinal product is not necessary if the product is already authorised. However, in this case, the published results of the authorisation can be used for the clinical assessment. If the technology encompasses the use of a pharmaceutical drug that is not yet authorised, this issue becomes of paramount importance and should be supervised by a legal counsel or legally trained pharmacist/chemist.

Aspect 6: Clinical Trials

Clinical trials can interfere with the rights of test persons (and animals) and have to meet not only ethical but also legal standards to be permitted and consequentially to be usable in HTAs for public authorities or other official bodies.

- A. Question:** Are any clinical trials of the technology planned or used in any part of the HTA (also in the clinical assessment)?
- B. Explanations:** The clinical assessment may include execution of new clinical trials. Such trials are also sometimes required by law, for example for the authorisation of medicinal products and medical devices (see above) or for proving eligibility for reimbursement in a public health care system (see below).

The law extensively regulates clinical trials, specifically by international and transnational norms. Purpose of these norms is mostly the protection of the right of patients as test persons. Among others these include the right to being asked for informed consent, data privacy, being not exposed to unnecessary tests, getting to know the details of tests as well as the test results if wanted. Failure to comply with the legal regulations can firstly cause legal and public liability towards the test persons and can secondly result in the uselessness of the conducted trials since the law forbids their use in authorisation procedures, reimbursement claims as well as for other purposes.

- F. Legal sources:** Most important legal sources on good practice in clinical trials are international conventions, particularly the Convention on Human Rights and Biomedicine, as well as European Directives, especially the Clinical Trial Directive 2001/20/EC, the

Directive on Good Clinical Practice 2005/28/EC, the Good Laboratory Practice Directive 2004/10/EC, and the Directive on Inspection and Verification of GLP 2004/9/EC. Corresponding national laws and directives have been passed by the Member States. For further explanation about EU wide regulation of research and development, see Chapter 9.3.

- C. Relations to other parts of the HTA: Naturally, this legal issue is strongly connected to the assessment of clinical implications of a technology. If clinical trials are planned or necessary for the assessment, the legal issue of regulation of clinical trials has to be considered before starting the trials to determine an appropriate study design. If no clinical trials are integral part of the HTA but already existing studies are used for the clinical or any other part of the assessment, it has to be ascertained that these comply with the legal provisions. Otherwise it is not unlikely that for example authorities will not accept the HTA report. Besides this, the legal issue regulation of clinical trials is inextricably linked with the ethical assessment as many of the legal rules on good practice in clinical trials are derived from or refer to ethical standards (such as the Helsinki Declaration).
- D. Relevant decision level and necessity of legal advice: The issue is only to be assessed if clinical trials are conducted or used for or in any part of the HTA. Consulting a legal counsel can be necessary if no clinician who is trained or at least experienced in this legal area is available. As the legal norms are closely related to ethical standards, an ethicist or moral philosopher dealing with this area can also be sufficient.

Aspect 7: Intellectual Property

Assessed technologies might either be protected by intellectual property laws or eligible for such protection, which can be either a hurdle or an advantage regarding the use of that technology.

- A. Question: Is the technology an (potential) invention? Is it protected or can it be protected under intellectual property laws?
- B. Explanations: In the sense of intellectual property law, an invention is a technology that is new, based on an inventive step and is susceptible to industrial application.

The technology in question might be protected by intellectual property measures, especially patents. If this is the case, application or production of the technology might constitute an infringement of these measures.

This can be avoided by obtaining a licence. If the technology in question is an invention and not protected as intellectual property, application for a patent or alike might be considered by the inventor.

- G. Legal sources: Intellectual property concerning inventions is regulated by inter- and supranational norms. Of high importance are the European Patent Convention and the European Regulation (EC) No. 469/2009. National acts are mostly corresponding to these and especially important for national patents (which again can be recognised by other countries under the rule of international law). For further information on the European regulation, see Chapter 9.3.
- C. Relations to other parts of the HTA: The question of intellectual property can be related to other legal as well as ethical issues as inventions that violate law or ethical standards are excluded from patentability.
- D. Relevant decision level and necessity of legal advice: This aspect can be of importance when medicinal products or medical devices are an integral part of the technology. The relevance, however, depends on the purpose of the HTA.

Example: In an assessment of a health insurance on whether an already authorised pharmaceutical drug is eligible for reimbursement by this insurance, the drug is most likely subject to intellectual property protection and the assessment of this issue is of minor or no importance. In an assessment conducted by a manufacturer on the question, whether a new drug might be eligible for authorisation, the issue of potential intellectual property conflicts and opportunities is of very high importance.

Aspect 8: Reimbursement in Public Health Care Systems

Whether or not a technology's use is reimbursed in a public health care system is of major importance for the successful usage and dissemination of that technology. Moreover, the question of reimbursement is often the question to be answered by HTA.

- A. Question: Is reimbursement by a public health care service intended or even subject to the HTA?
- B. Explanations: In many countries of the European Union, the public health care system is an important, if not the most important supplier for health care services. These systems might be designed as public, tax-financed systems like the National Health Service in UK, or public health insurance funds like the Statutory Health Insurance in Germany. Because of their

paramount importance for the delivery of health services (close to 90 % of all Germans are members of the public health insurance funds), being eligible for reimbursement by the public health care systems is often crucial for the 'success' of a technology.

Because of financial restraints, every public health care system has developed mechanisms for the rationing or rationalising: technologies have to meet certain legal standards to be eligible for reimbursement. These standards mostly concern the safety, clinical effectiveness, benefit/risk-ratio of the technology in question. Moreover, new technologies often have to prove that they have an additional value in comparison to already existing and reimbursed alternative therapies or technologies. Although the legal prerequisites refer to medicinal or economical standards they do not necessarily fall together with these and, in the case of medical devices and medicinal products, are especially not limited to the standards of authorisation.

C. Legal sources: The catalogue of services of a public health care service is exhaustively regulated on the national level. Because of the rapid development of new health technologies and the resulting possible treatments the decision on which of these are reimbursed cannot be made by the legislation by the means of a law. The law however appoints competent bodies or authorities (e.g. the Federal Joint Committee in Germany or NHS England and Public Health England in UK). These substantiate the relatively abstract and unspecific legal requirements on health care services and with that are responsible for the appropriate use of the available budget. The decisions are mostly based on data and evidence provided by independent institutions (such as NICE in UK and IQWiG in Germany). These sub-legal regulations are legally binding and have to be considered in the assessment.

Relations to other parts of the HTA: The decision on reimbursement of health technologies can be based on the result of the complete HTA. Although the results of the clinical and economic assessment are often of paramount importance for the decision, other issues such as socio-cultural or ethical issues have to be considered as well. Insofar this issue is often related to all other parts of the HTA.

Example: The question whether a the treatment with a pain-relieving but life-shortening drug in palliative care shall be paid for by the public health care system can probably not be decided on clinical and economic grounds only. If a society ethically and culturally values its own duty to protect the life of the individual higher

than the possibility of pain-relief, considerations of clinical effectiveness are likely to be insufficient to rule on the issue of reimbursement.

D. Relevant decision level and necessity of legal advice: The issue of reimbursement by public health care systems is often the purpose of an HTA: The decision on whether a technology is eligible for reimbursement can be based on the results of the assessment of this technology. In this case the assessment of the legal issue of reimbursement has to be conducted before the actual assessment to clarify the legal prerequisites for reimbursement beforehand. As legal provisions on reimbursement are very diverse and often not comprehensible to non-lawyers, consulting legal counsel is mandatory. However, if the object of the HTA is a technology already included in the catalogue of service of the public health care system, the assessment of this issue can be forgone.

E. Relevant decision level and necessity of legal advice: The issue of reimbursement by public health care systems is often the purpose of an HTA: The decision on whether a technology is eligible for reimbursement can be based on the results of the assessment of this technology. In this case the assessment of the legal issue of reimbursement has to be conducted before the actual assessment to clarify the legal prerequisites for reimbursement beforehand. As legal provisions on reimbursement are very diverse and often not comprehensible to non-lawyers, consulting legal counsel is mandatory. However, if the object of the HTA is a technology already included in the catalogue of service of the public health care system, the assessment of this issue can be forgone.

Aspect 9: Special Medical Fields

Some technologies are applied in medical fields of high sensitivity, which are therefore regulated by special laws. In these fields a higher number of legal questions arises with the (intended) use of the technology what makes a very thoroughly assessment of legal aspects necessary.

A. Question: Is the technology applied in a special medical field?

B. Explanations: Special medical fields are subject to special legal regulation due to particular problems in these fields. This often is the case in fields that are ethically or socially controversially discussed or in which the risk for the patient is particularly high.

Example: The question of organ allocation in transplantation medicine is not only controversially discussed in

many countries because of ethical and cultural concerns but is also associated to other issues such as potentially high clinical risks for donors as well as recipients or illegal organ trade. Transplantation medicine is therefore highly regulated.

Similar examples are prenatal screening as well as other fields concentrating on mothers and the nasciturus, genetic testing, palliative care, orphan diseases,

The legal aspects connected to special medical fields are as diverse as these fields and cannot be presented here. However, due to the high importance societies attach to these fields, negligence of the respective legal regulations can result in severe legal consequences including penalties according to criminal law.

C. Legal sources: Legal sources for the regulation of special medical fields are as diverse as these fields and cannot be presented here. These very sensitive fields are often dependent on certain societal values and therefore subject to national legislation, such as the Human Tissue Acts in UK or the Law on Genetic Diagnostics (Gendiagnostikgesetz) in Germany. However, in cases in which different societies agree on common standards and in which regulation on the international level is also more promising, international norms might apply as well. On the other hand, internationalisation of the regulation of such fields can cause ethical concerns.

Example: The allocation of human organs through Eurotransplant in Austria, Belgium Croatia, Germany, Hungary, Luxembourg, the Netherlands and Slovenia makes it more likely to connect donor and recipient but also raises questions of the national character of solidarity in health care systems.

D. Relations to other parts of the HTA: As special medical fields are often characterised by a high potential for ethical and social conflicts, the assessment of ethical and socio-cultural issues can be used to identify these fields.

E. Relevant decision level and necessity of legal advice: The legal norms on special medical fields constitute rules of extreme diversity and scope with major impact on the use of a technology. The question whether the technology of question is applied in such a field is therefore of paramount importance and should be clarified. If a special medical field is affected, a legal counsel should be consulted urgently.

6.4 CONCLUSIONS

6.4.1 Main insights

Nine legal core issues may potentially be considered within an HTA. Which of these are of relevance for a specific technology and which are assessed in a specific context can be basically determined by using this framework.

6.4.2 Strengths and limitations of current method

Using this guidance allows identification of potentially relevant legal core issues within an HTA. HTA conductors without profound legal training can get an overview about which issues can be addressed in an HTA and which connections can be made between the assessment of these legal aspects and other (also non-legal) issues. By pointing out these connections as well as the relevance of each issue for different levels of decision-making, this guidance aims to avoid unnecessary (for example multiple) assessments of aspects of minor importance for the specific HTA. However, it is clear that non-lawyers cannot conduct a complete assessment of a specific legal issue only by using the guidance. Such an assessment requires profound legal skills and has to be based on the specifications of a specific technology. If an aspect is, based on this guidance, considered as relevant for the HTA but the specific implications of that aspect seem to be unclear, only advice of a qualified legal counsel can bring legal certainty. Moreover, this generic guidance cannot cover every possibly important legal issue. Other aspects than the nine core aspects elaborated on in this guidance might be of importance.

6.4.3 Outlook

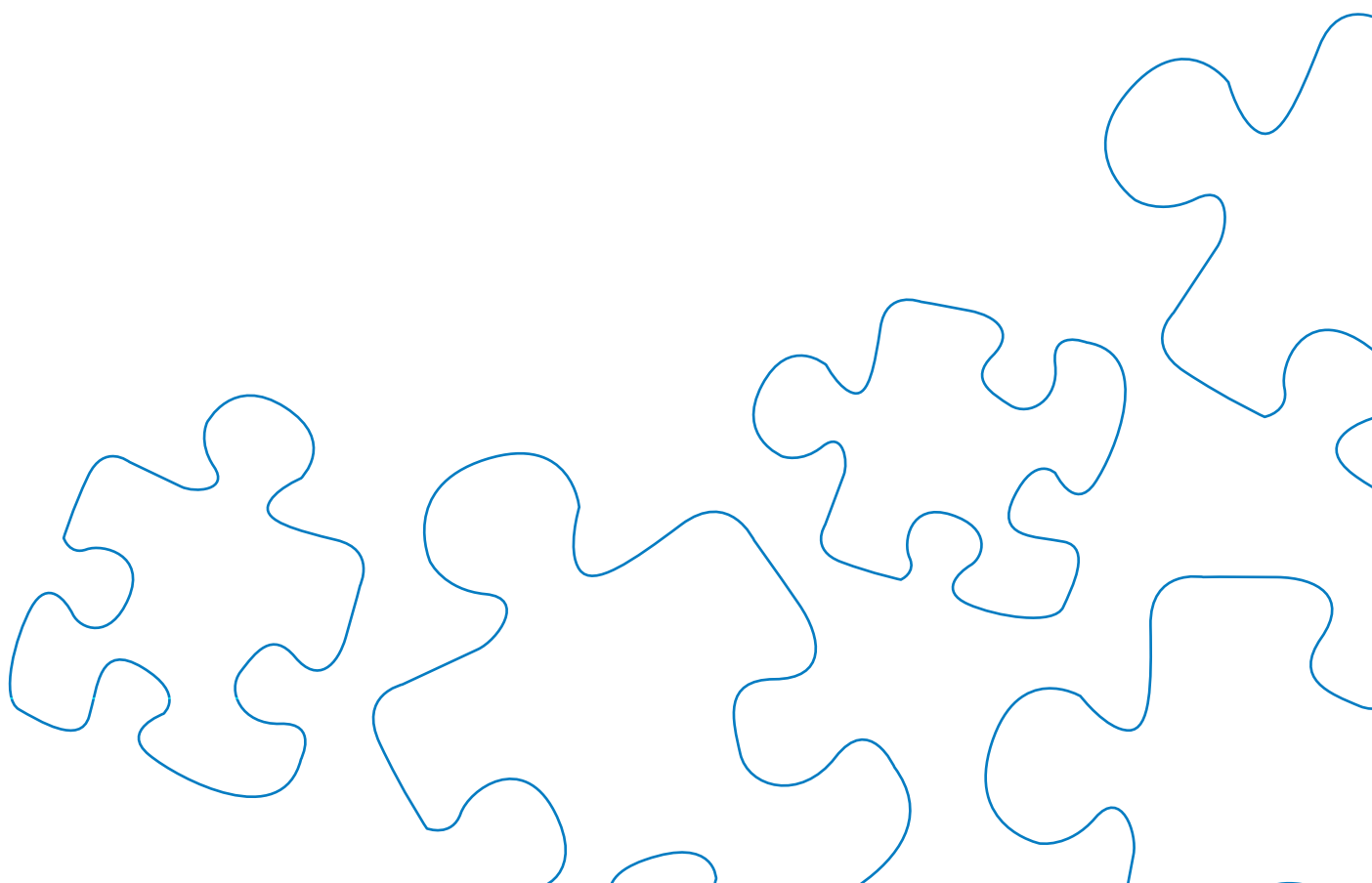
Despite the limitations of this guidance, we hope that it can help getting a basic understanding of potential legal implications of health technologies. If non-legally trained HTA-conductors bear these issues in mind, basic legal risks can be avoided and this can greatly improve the impact of an HTA.

7 ACKNOWLEDGEMENT

We would like to thank all those who contributed to the establishment of this guidance: external experts, stakeholders who participated in the case study and members of the INTEGRATE-HTA project. We also thank the European Union for funding this project.

The guidance was reviewed from the following external experts: David Banta, Eva Bitzer, Aurelija Blaževičienė, Sigrid Droste, Iñaki Imaz-Iglesia, Kristian Lampe, Pascale Lehoux, Marco Marchetti, Sheila Payne, Brügger Urs, Ingrid Wilbacher and Claudia Wild.

Furthermore we would like to thank all those who are not explicitly mentioned here because of reasons of anonymity.



8 REFERENCES

- ABELSON, J., EYLES, J., MCLEOD, C.B., COLLINS, P., MCMULLAN, C., FOREST, P.G. (2003) Does deliberation make a difference? Results from a citizens panel study of health goals priority setting. *Health Policy*, 66, 95-106.
- ABELSON, J., GIACOMINI, M., LEHOUX, P., GAUVIN, F.P. (2007) Bringing 'the public' into health technology assessment and coverage policy decisions: From principles to practice. *Health Policy*, 82, 37-50.
- ABRISHAMI, P., BOER, A., HORSTMAN, K. (2015) How can we assess the value of complex medical innovations in practice? *Expert Rev. Pharmacoecon. Outcome Res*, 15, 369-371.
- ANDERSON, L.M., OLIVER, S.R., MICHIE, S. (2013) Investigating complexity in systematic reviews of interventions by using a spectrum of methods. *J Clin Epidemiol*, 66, 1223-9.
- ANDERSON, L.M., PETTICREW, M., CHANDLER, J., et al. (2013) Introducing a series of methodological articles on considering complexity in systematic reviews of interventions. *J Clin Epidemiol*, 66, 1205-8.
- ARELLANO, L.E., REZA, M., BLASCO, J.A., ANDRADAS, E. (2009) A content analysis of health technology assessment programs in Latin America. *Int J Technol Assess Health Care*, 570-576.
- ARTHUR, W.B. (2013) Complexity Economics: A different framework for economic thought. SFI Working Paper: 2013-04-012. [Online]. Available from: <http://www.santafe.edu/media/workingpapers/13-04-012.pdf>
- ASSASI, N., SCHWARTZ, L., TARRIDE, J. E., CAMPBELL, K., GOEREE, R. (2014) Methodological guidance documents for evaluation of ethical considerations in health technology assessment: a systematic review. *Expert Review of Pharmacoeconomics & Outcomes Research*, 14, 203-220.
- BANTA, D. (1993) Assessing social implications of health care technology. In: BANTA, D., LUCE, B. (eds.). *Health Care Technology and its Assessment. An International Perspective*. Oxford: Oxford University Press.
- BARDIA, A., PAUL, E., KAPOOR, S.K., ANNAND, K. (2004) Declining sex ratio: Role of society, technology and government regulation in Faridabad district, Haryana. *National Medical Journal of India*, 17, 207-211.
- BARKER, C. (2004) *The SAGE Dictionary of Cultural Studies*. London: Sage Publications Ltd.
- BARMEYER, C. (2010) Kultur in der interkulturellen Kommunikation. In: BARMEYER, C., GENKOVA, P., SCHEFFER, J. (eds.). *Interkulturelle Kommunikation und Kulturwissenschaft. Grundbegriffe, Wissenschaftsdisziplinen, Kulturräume*. Passau: Verlag Karl Stutz.
- BATTISTA, R.N., HODGE, M.J. (1999) The evolving paradigm of health technology assessment: Reflections for the millennium, *Canadian Medical Association Journal*, 160, 1464-1467.
- BAUER, K. A. (2002) *The Ethical Implications of Telemedicine and the Internet for Home Healthcare*. PhD diss.
- BEAUCHAMP, T. L., CHILDRESS, J. F. (2001) *Principles of biomedical ethics* (5 ed.). New York: Oxford university press.
- BECK, U. (1992) *Risk Society: Towards a New Modernity*. New Delhi: Sage.
- BERG, B.L. (2009) *Qualitative research methods for the social sciences*. Boston: Allyn & Bacon.
- BOOTH, A., NOYES, J., FLEMMING, K., GERHARDUS, A., WAHLSTER, A., VAN DER WILT, G.J., MOZYGEMBA, K., REFOLO, P., SACCHINI, D., TUMMERS, M., REHFUESS, E. (2016) Guidance on choosing qualitative evidence synthesis methods for use in health technology assessments of complex interventions [Online]. Available from: <http://www.integrate-hta.eu/downloads/>
- BORENSTEIN, M., HEDGES, L., HIGGINS, J., ROTHSTEIN, H. (2009) *Introduction to meta analysis: statistics in practice*. Chichester, UK: Wiley.
- BOURDIEU, P. (1977) *Outline of a Theory of Practice*. Cambridge: Cambridge University Press.
- BRAUNACK-MAYER, A., PALMER, N. (2008) Health Technology Assessment: Ethical, Legal and Social Issues, p. 265-269. In: Heggenhougen, K., Quah, S.R. (eds.), *International Encyclopedia of Public Health*. San Diego, Academic Press.

- BRAZIER, J., TSUCHIYA, A. (2015) Improving Cross-Sector Comparisons: Going Beyond the Health-Related QALY. *Applied health economics and health policy*, 1-9.
- BRENNAN, A., CHICK, S.E., DAVIES, R. (2006) A taxonomy of model structures for economic evaluation of health technologies. *Health Econ* 15,1295-1310.
- BRERETON, L., WAHLSTER, P., LYSDAHL, K.B., MOZYGEMBA, K., BURNS, J., CHILCOTT, J.B., WARD, S., BRÖNNEKE, J.B., TUMMERS, M., VAN HOORN, R., PFADENHAUER, L., POLUS, S., INGLETON, C., GARDINER, C., VAN DER WILT, G.J., GERHARDUS, A., ROHWER, A., REHFUESS, E., OORTWIJN, W., REFOLO, P., SACCHINI, D., LEPPERT, W., BLAZEVICIENE, A., SPAGNOLO A.G., PRESTON, L., CLARK, J., GOYDER, E., ON BEHALF OF THE INTEGRATE-HTA TEAM (2016) Integrated assessment of home based palliative care with and without reinforced caregiver support: 'A demonstration of INTEGRATE-HTA methodological guidances' [Online]. Available from: <http://www.integrate-hta.eu/downloads/>
- BRIDGES, J.F., JONES, C. (2007) Patient-based health technology assessment: A vision of the future. *Int J Technol Assess Health Care*, 23, 30-35.
- BUCHANAN, A. X., BROCH, D. W., DANIELS, N., & WIKLER, D. (2000) *From Chance to Choice: Genetics and Justice*. Cambridge: Cambridge University Press.
- BURFORD, B., LEWIN, S., WELCH, V., et al. (2013) Assessing the applicability of findings in systematic reviews of complex interventions can enhance the utility of reviews for decision making. *J Clin Epidemiol.*, 66,1251-61.
- BURKE, W., ZIMMERN, R. (2007) Moving beyond ACCE: An Expanded Framework for Genetic Test Evaluation, A Paper for the United Kingdom Genetic Testing Network [Online]. Available from: <http://www.phgfoundation.org/reports/4971/> [Accessed: 21.06.2015].
- BURNS, J., BOOGARD, H., TURLEY, R. (2014) Interventions to reduce particulate matter air pollution and their effect on health. *Cochrane Database of Systematic Reviews*, (Issue 1. Art No., CD010919).
- BUSSE, R., ORVAIN, J., VELASCO, M., PERLETH, M., DRUMMOND, M., GÜRTNER, F., JORGENSEN, T., JOVELL, A., MALONE, J., RÜTHER, A., WILD, C. (2002) Best practice in undertaking and reporting HTA. *Int J Technol Assess Health Care*, 18, 361-422.
- BUXTON, M., DRUMMOND, M., VAN HOUT, B., PRINCE, R., SHELDON, T., SZUCS, T., VRAY, M. (1997) Modelling in economic evaluation: an unavoidable fact of life. *Health Economics*, 6, 217-227.
- CAPRI, S., CECI, A., TERRANOVA, L., MERLO, F., MANTOVANI, L. (2001). Guidelines for economic evaluation in Italy; Recommendations from the Italian group of pharmacoeconomic studies. *Drug Information Journal*, 35, 189-201.
- CAVAZZA, M., JOMMI, C. (2012) Stakeholder involvement by HTA Organisations: Why is so different? *Health Policy*, 105, 236-245.
- CHECKLAND, P., SCHOLE, J. (1999) *Soft Systems Methodology in Action*. John Wiley & Sons.
- CHILCOTT, J., TAPPENDEN, P., RAWDIN, A., JOHNSON, M., KALTENTHALER, E., PAISLEY, S., PAPAIOANNOU, D., SHIPPAM, A. (2010) Avoiding and identifying errors in health technology assessment models. *Health Technology Assessment*, 14.
- CLAUSEN, C., YOSHINAKA, Y. (2004) Social shaping of technology in TA and HTA. *Poiesis & Praxis*, 2, 221-246.
- COAST, J., SMITH, R., & LORGELLY, P. (2008) Should the capability approach be applied in health economics?. *Health economics*, 17, 667-670.
- COCHRANE – About us. (2014) The Cochrane Collaboration website <http://www.cochrane.org/about-us>. [Accessed: 18.02.2015]
- COCHRANE PUBLIC HEALTH – For Review Authors (2015) Guidance for establishing and managing Review Advisory Groups [online]. Available from: <http://ph.cochrane.org/review-authors> [Accessed: 07.07.2015].
- COCHRANE COLLABORATION, C. Cochrane Community (beta) [Online].

- COLLEGE VOOR ZORGVERZEKERINGEN. (2006) Guidelines for pharmacoeconomic research, updated version. Valid from April 1st 2006 [online]. Available from: <http://www.zorginstituutnederland.nl/>.
- COTTON, M. (2009) Ethical assessment in radioactive waste management: a proposed reflective equilibrium based deliberative approach. *Journal of Risk Research*, 12(5), 603-618.
- CRAIG, P., DIEPPE, P., MACINTYRE, S., MICHIE, S., NAZARETH, I., PETTICREW, M. (2008) Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ*, 337: 979-983.
- DAKE, K., THOMPSON, M. (1999) The Meaning of sustainable development: household strategies for managing needs and resources. In: WRIGHT, S.D., DIETZ, T., BORDEN, R., YOUNG, G., GUAGNAO, G. (eds.). *Human Ecology: Crossing Boundaries*. Fort Collins: The Society for Human Ecology.
- DALKEY, N., HELMER, O. (1963) An experimental application of the Delphi Method to the use of experts. *Management Science*, 9, 458-467.
- DANIELS, N. (1979) Wide Reflective Equilibrium and Theory Acceptance in Ethics. *Journal of Philosophy*, 76(5), 256-282.
- DANIELS, N. (2013) Reflective Equilibrium [online]. Available from: <http://plato.stanford.edu/archives/win2013/entries/reflective-equilibrium/> [Accessed: 14.10.2014]
- DAVIS, C., TOMAS, J. (2014) Care of the dying: how do we replace the Liverpool Care Pathway? *British Medical Bulletin*, 112(1), 5-15.
- DE SAVIGNY, D., ADAM, T. (eds). (2009) *Systems thinking for health systems strengthening*. Alliance for Health Policy and Systems Research, WHO.
- DEEKS, J.J., DINNES, J., D'AMICO, R., et al. (2008) Evaluating non-randomised intervention studies. *Health Technol Assess*. 7.
- DELBECQ, A.L., VAN DE VEN, A.H. (1971) A Group Process Model for Problem Identification and Program Planning. *Journal of Applied Behavioral Science*, 4, 466-491.
- DELBECQ, A.L., VAN DE VEN, A.H., H., G.D. (1975) *Group technique for program planning: a guide to nominal group and Delphi processes*. Glenview: Scott Foresman and Company.
- DOUGLAS, M. (1978) *Cultural bias*. London: Royal Anthropological Institute of Great Britain and Ireland.
- DRABORG, E., GYRD-HANSEN, D., POULSEN, P.B., HORDER, M. (2005) International comparison of the definition and the practical application of health technology assessment. *Int J Technol Assess Health Care*, 21, 89-95.
- DROSTE, S. (2010) Integrating ethical issues in HTAs: More methods than applications? Paper presented at the HTAi 7th Annual Meeting, Maximising the Values of HTA, Dublin.
- DROSTE, S., Dintsios, C. M., Gerber, A. (2010). Information on ethical issues in health technology assessment: how and where to find them. *Int J Technol Assess Health Care*, 26, 441-449.
- DROSTE, S., Herrmann-Frank, A., Scheibler, F., Krones, T. (2011) Ethical issues in autologous stem cell transplantation (ASCT) in advanced breast cancer: a systematic literature review. *BMC Medical Ethics*, 12, 6.
- DRUMMOND, M.F., SCULPHER, M.J., TORRANCE, G.W., O'BRIEN, B.J., STODDART, G.L. (2005) *Methods for the Economic Evaluation of Health Care Programmes*.
- ECCLES, M., CLAPP, Z., GRIMSHAW, J., et al. (1996) North of England evidence based guidelines development project: methods of guideline development. *BMJ*, 312, 760-762.
- EDEN, C., ACKERMANN, F. (2004). Cognitive mapping expert views for policy analysis in the public sector. *European Journal of Operational Research*, 152 (3): 615-630.
- ELDESSOUKI, R., SMITH, M.D. (2012). Health care system information sharing: A step toward better health globally. *Value in Health ,Regional Issues* 1: 118-29.
- ELLERIN, B.E., SCHNEIDER, R.J., STERN, A., TONIOLO, P.G., FORMENTI, S.C. (2005) Ethical, Legal and Social Issues Related to Genomics and Cancer Research: The Impending Crisis, *Journal of the American College of Radiology*, 2:11, 919-126.

- ENGELKE, K., DROSTE, S. (2014) Bewertung der rechtlichen Aspekte von Technologien. In: Perleth, M. et al. (eds.), Health Technology Assessment (2 ed.)
- EPOC, Cochrane Effective Practice and Organisation of Care Group. Study designs accepted in EPOC reviews. <http://epocoslo.cochrane.org/epoc-specific-resources-review-authors> [Accessed: 17.04.2013].
- EUnetHTA (2015) EUnetHTA Joint Action 2, Work Package 8. HTA Core Model © version 3.0 PUBLIC DRAFT (Pdf)
- EUnetHTA (2015) EUnetHTA Joint Action 2, Work Package 8. HTA Core Model © version 2.1 [Online]. Available from: <http://www.corehta.info/BrowseModel.aspx>.
- EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT. (2008) HTA core model for medical and surgical interventions.
- EUnetHTA. EUnetHTA Adaptation Glossary (beta) [Online]. Available from: <http://www.eunethta.be/glossary/?-q=glossary/c>.
- FACEY, K., GRANDADOS, A., GUYATT, G., et al. (2014) Generating health technology assessment evidence for rare diseases. *Int J Technol Assess Health Care.*, 30, 416-22.
- FARRELL, A., VANDEVEER, S.D., JÄGER, J. (2001) Environmental assessments: four under-appreciated elements of design. *Global Environmental Change*, 11, 311-333.
- FISCHER, F. (1995) *Evaluating Public Policy*. Chicago: Nelson-Hall.
- FRANCO, L.A. (2006) Forms of conversation and problem structuring methods: a conceptual development. *Journal of the Operational Research Society*, 57(7):813-821.
- FREEMAN, C. (1995) Preface. In: RIP, A., MISA, T., SCHOT, J. (eds.). *Managing technology in society. The approach of Constructive Technology Assessment*. London: Pinter Publishers.
- GAGNON, M.-P., DESMARTIS, M., LEPAGE-SAVARY, D., GAGNON, J., ST-PIERRE, M., RHAINDS, M., LEMIEUX, R., GAUVIN, F.-P., POLLENDER, H., LÉGARÉ, F. (2011) Introducing patients' and the public's perspectives to health technology assessment: A systematic review of international experiences. *Int J Technol Assess Health Care*, 27, 31-42.
- GALLO, P. (2004) Integrating ethical enquiry and health technology assessment: limits and opportunities for efficiency and equity. *Poiesis & Praxis*, 2, 103-117.
- GAUVIN, F.-P., ABELSON, J., GIACOMINI, M., EYLES, J., LAVIS, J.N. (2010) "It all depends": Conceptualizing public involvement in the context of health technology assessment agencies. *Social Science and Medicine*, 70, 1518-1526.
- GERHARDUS, A., STICH, A.K. (2008) Sozio-kulturelle Aspekte in Health Technology Assessments (HTA). *Zeitschrift für Evidenz, Fortbildung und Qualität im Gesundheitswesen*, 102, 77-83.
- GERHARDUS, A., STICH, A.K. (2014) Die Bewertung sozio-kultureller Aspekte im HTA. In: PERLETH, M., BUSSE, R., GERHARDUS, A., GIBIS, B., LÜHMANN, D., ZENTNER, A. (eds.). *Health Technology Assessment. Konzepte, Methoden, Praxis für Wissenschaft und Entscheidungsfindung*. Berlin: MWV Medizinisch Wissenschaftliche Verlagsgesellschaft.
- GIBSON, B. E., SECKER, B., ROLFE, D., WAGNER, F., PARKE, B., MISTRY, B. (2012) Disability and dignity-enabling home environments. *Social Science and Medicine*, 74(2), 211-219.
- GLENTON, C., LEWIN, S., MAYHEW, A., et al. (2013) Nonrandomized studies are not always found even when selection criteria for health systems intervention reviews include them: a methodological study. *J Clin Epidemiol*, 66, 367-370.
- GOEL, V. (2001) Appraising organised screening programmes for testing for genetic susceptibility to cancer. *British Medical Journal*, 322, 1174-1178.
- GOLD, M.R., SIEGAL, J.E., RUSSELL, L.B., WEINSTEIN, M.C. et al. (eds.) (1996) *Cost-effectiveness in health and medicine*. Oxford: Oxford University Press.

- GOMES, B., CALANZANI, N., CURIALE, V., MCCRONE, P., & HIGGINSON, I.J. (2013). Effectiveness and cost-effectiveness of home palliative care services for adults with advanced illness and their caregivers. *Cochrane Database Syst Rev*, (6;CD007760).
- GOUDET, SM., GRIFFITHS, PL., BOGIN, B.A., MADISE, N.J. (2015) Nutritional interventions for preventing stunting in children (0 to 5 years) living in urban slums. *Cochrane Database of Systematic Reviews* (Issue 5).
- GRIMES, DA., SCHULZ, K.F. (2002) An overview of clinical research: the lay of the land. *Lancet*, 359, 57-61.
- GRADE Working Group. (2004) Grading quality of evidence and strength of recommendations. *BMJ*. 328, 1490.
- GRANT, M.J., BOOTH, A. (2009) A typology of reviews: an analysis of 14 review types and associated methodologies. *Health Information and Libraries Journal*, 26, 91-108.
- GRIN, J., GRAAF, H. V. D., HOPPE, R. (1997) Technology assessment through interaction: a guide Working document Rathenau Institute; W57.
- GUYATT, G.H., OXMAN, A.D., VIST, G.E., et al. (2008) GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*, 336, 924-6.
- GUYATT, G.H., OXMAN, A.D., SCHÜNNEMANN, H.J., et al. (2011) GRADE guidelines: A new series of articles in the *Journal of Clinical Epidemiology*. *J Clin Epidemiol*, 64, 380-382.
- HANNES, K., LOCKWOOD, C., (2012) *Synthesizing Qualitative Research: Choosing the Right Approach*. Chichester, UK: Wiley-Blackwell.
- HEINTZ, E., LINTAMO, L., HULTCRANTZ, M., JACOBSON, S., LEVI, R., MUNTHE, C., SANDMAN, L. (2015). Framework for systematic identification of ethical aspects of healthcare technologies: the sbu approach. *Int J Technol Assess Health Care*, 1-7.
- HIGGINS, J.P.T., GREEN, S. (eds.).(2011) *Cochrane Handbook for Systematic Reviews of Interventions*, Version [5.1.0] (updated March 2011). The Cochrane Collaboration [Online]. Available from: www.cochrane-handbook.org [Accessed: 07.08.2013].
- HIGGINS, J.P.T., RAMSAY, C., REEVES, B.C., et al. (2012) Issues relating to study design and risk of bias when including non-randomized studies in systematic reviews on the effects of interventions. *Res Synth Methods*, 25, 12-25.
- HOFMANN, B. (2001) The paradox of health care. *Health Care Analysis*, 9(4), 369-386.
- HOFMANN, B. (2005) Toward a procedure for integrating moral issues in health technology assessment. *Int J Technol Assess Health Care*, 21(3), 312-318.
- HOFMANN, B. (2012). Ethical Challenges with Welfare Technology: A Review of the Literature. *Sci Eng Ethics*.
- HOFMANN, B., DROSTE, S., OORTWIJN, W., CLEEMPUT, I., SACCHINI, D. (2014). Harmonization of ethics in health technology assessment: a revision of the socratic approach. *Int J Technol Assess Health Care*, 30(1), 3-9.
- HOFMANN, B., HJELMESAETH, J., SOVIK, T. T. (2013) Moral challenges with surgical treatment of type 2 diabetes. *Journal of Diabetes and Its Complications*, 27(6), 597-603.
- HOFMANN, B., LYSDAHL, K. B., DROSTE, S. (2015b) Evaluation of ethical aspects in health technology assessment: more methods than applications? *Expert Review of Pharmacoeconomics & Outcomes Research*, 15(1), 5-7.
- HOFMANN, B., OORTWIJN, W., BAKKE LYSDAHL, K., REFOLO, P., SACCHINI, D., VAN DER WILT, G. J., GERHARDUS, A. (2015a) Integrating ethics in health technology assessment: many ways to Rome. *Int J Technol Assess Health Care*, 1-7.
- HOFMANN, B., SOLBAKK, J. H., & HOLM, S. (2006) Analogical reasoning in handling emerging technologies: the case of umbilical cord blood biobanking. *Am J Bioeth*, 6(6), 49-57.
- HUSEREAU, D., JACOBS, P., MANNS, B., HOOMANS, T., MARSHALL, D., TAMBLYN, R. (2014) *Economic Evaluation of Complex Health System Interventions: A Discussion Paper*. Institute of Health Economics [Online]. Available from: <http://www.ihe.ca/publications/economic-evaluation-of-complex-health-system-interventions-a-discussion-paper>

- HYDE, M., POWER, D. (2006) Some ethical dimensions of cochlear implantation for deaf children and their families. *J Deaf Stud Deaf Educ*, 11, 102-111.
- INAHTA, HTAi, AL., E. HTA Glossary.net [Online]. Available from: <http://htaglossary.net/List+all+terms>.
- INTERNATIONAL NETWORK OF AGENCIES FOR HEALTH TECHNOLOGY ASSESSMENT (INAHTA). (2015) HTA Glossary [Online]. Available from: <http://htaglossary.net/HomePage> [Accessed: 23.10.2015].
- INSTITUT FÜR QUALITÄT UND WIRTSCHAFTLICHKEIT IM GESUNDHEITSWESEN (IQWiG). (2009) General Methods for the Assessment of the Relation of Benefits to Costs. Version 1.0–19/11/2009 [Online]. Available from: <https://www.iqwig.de>
- INSTITUTE OF HEALTH ECONOMICS. (2012) Bariatric treatments for adult obesity. Edmonton AB: Institute of Health Economics.
- ITALIA, N., REHFUESS, E.A. (2012) Is the Global Solar UV Index an effective instrument for promoting sun protection? A systematic review. *Health Educ Res.*, 27, 200-13.
- JACKSON, D., RILEY, R., WHITE, I.R. (2011) Multivariate meta-analysis: Potential and promise. *Stat Med*. 26 January. 30: 2481-2498.
- JANSSEN, I.M., GERHARDUS, A., SCHROER-GUNTHER, M.A., SCHEIBLER, F. (2014) A descriptive review on methods to prioritize outcomes in a health care context. *Health Expect*.
- JORGENSSON, M.S., JORGENSSON, U., CLAUSEN, C. (2009) The social shaping approach to technology foresight. *Futures*, 41, 80-86.
- KALTENTHALER, E., TAPPENDEN, P., PAISLEY, S. (2011) Identifying and reviewing evidence to inform the conceptualisation and population of cost- effectiveness models., University of Sheffield, Sheffield, UK.
- KHAN, K.S., TERRIET, G., GLANVILLE, J., SOWDEN, A.J., KLEIJNEN, J. (2008) Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews. York: NHS Centre for Reviews and Dissemination, University of York.
- KIRCH, W. (ed.) (2008) *Encyclopedia Public Health*. Dordrecht: Springer Science+Business Media, LLC.
- KMET, L., LEE, R.C., COOK, L.S., LORENZETTI, D., GODLOVITCH, G., EINSIEDEL, E. (2004) *Systematic Review of the Social, Ethical, and Legal Dimensions of Genetic Cancer Risk Assessment Technologies*. Edmonton: AHFMR.
- KOMDUUR, R. (2013) Considering the path of nutrigenomics: a pragmatic ethical approach. PhD thesis. Wageningen: Wageningen University.
- KRISTENSEN, F.B., SIGMUND, H. (eds.) (2007) *Health Technology Assessment Handbook*. Copenhagen: National Board of Health, Denmark, DACEHTA - Danish Centre for Health Technology Assessment.
- KROESE, M., ZIMMERN, R.L., FARNDON, P., STEWART, F., WHITTAKER, J. (2007) How can genetic test be evaluated for clinical use? Experience of the UK Genetic Testing Network. *European Journal of Human Genetics*, 15:9, 917-921.
- LAMPE, K., MAKELA, M., GARRIDO, M. V., ANTTILA, H., AUTTI-RAMO, I., HICKS, N. J. European network for Health Technology, A. (2009a) The HTA Core Model: a novel method for producing and reporting health technology assessments. *Int J Technol Assess Health Care*, 25 Suppl 2, 9-20.
- LAMPE, K., MAKELA, M., GARRIDO, M. V., ANTTILA, H., AUTTI-RAMO, I., HICKS, N. J. European network for Health Technology, A. (2009b) The HTA Core Model: a novel method for producing and reporting health technology assessments. *Int J Technol Assess Health Care*, 25 Suppl 2, 9-20.
- LEE, A., SKÖTT, L.S., HANSEN, H.P. (2009) Organizational and patient-related assessments in HTAs: State of the art. *Int J Technol Assess Health Care*, 25, 530-536.
- LEHOUX, P., TAILLIEZ, S., DENIS, J.L., HIVON, M. (2004) Redefining health technology assessment in Canada: Diversification of products and contextualization of findings. *Int J Technol Assess Health Care*, 20, 325-336.
- LEHOUX, P., WILLIAMS-JONES, B. (2007) Mapping the integration of social and ethical issues in health technology assessment. *Int J Technol Assess Health Care*, 23, 9-16.

- LINSTONE, H.A., TUROFF, M. (1975) The Delphi Method: Techniques and Applications. Reading: Addison-Wesley.
- LYSDAHL, K.B., DROSTE, S. (2015) Ethical analysis. [Online]. Available from: <http://vortal.htai.org/?q=node/11> [Accessed: 17.11.2015].
- MAMADOUH, V. (1999) A political-cultural map of Europe. Family structures and the origins of differences between national political cultures in the European Union. *GeoJournal*, 47, 477-486.
- MARMOT, M., WILKINSON, R.G. (eds.) (1999) Social determinants of health. Oxford: Oxford University Press.
- MEDCOM & NORWEGIAN CENTRE FOR INTEGRATED CARE AND TELEMEDICINE (2010) MethoTelemed. Methodology to assess telemedicine applications [Online]. Available from: www.telemed.no/methotelemed [Accessed: 10.06.2014].
- MEDICAL RESEARCH COUNCIL, UK (MRC) (2008). Developing and evaluating complex interventions: new guidance [online] Available from: <http://www.mrc.ac.uk/documents/pdf/complex-interventions-guidance/> [Accessed: 21.07.2015].
- MINGERS, J., GILL, A.(eds.) (1997) Multimethodology: The theory and practice of combining management science methodologies. Chichester., Wiley.
- MITROFF, I.I., FEATHERINGHAM, T.R. (1974) On systemic problem solving and the error of the third kind. *Behavioral Science*, 19, 383-393.
- MOORE, G.F., AUDREY, S., BARKER, M., et al. (2015) Process evaluation of complex interventions: Medical Research Council Guidance. *BMJ*, 350, h1258.
- MOSSIALOS, E., THOMSON, S., TER LINDEN, A. (2004) Information technology law and health systems in the European Union. *Int J Technol Assess Health Care*, 20:4, 498-508.
- NHMRC (1998) A guide to the development, implementation and evaluation of clinical practice guidelines. National Health and Medical Research Council. November 16. NHMRC, Commonwealth of Australia.
- NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE (NICE) (2008) Social Value Judgements. Principles for the development of NICE guidance. (2 ed). London: NICE.
- NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE (NICE). (2009). Methods for development of NICE public health guidance (2 ed.). National Institute for Health and Clinical Excellence.
- NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE (NICE) (2013). Guide to the methods of technology appraisal. [online] Available from: <http://publications.nice.org.uk/pmg9> [Accessed: 27.10 2014]
- NIELSEN, C.P., WADMANN LAURITSEN, S., KRISTENSEN, F.B., BISTRUP, M.L., CECCHETTI, A., TURK, E. (2009) Involving stakeholders and developing a policy for stakeholder involvement in the European network for Health Technology Assessment, EUnetHTA. *Int J Technol Assess Health Care*, 25, 84-91.
- NIGENDA, G., LANGER, A., KUCHAISIT, C., ROMERO, M., ROJAS, G., AL-OSIMY, M., VILLAR, J., GARCIAS, J., AL-MAZROU, Y., BA'AQEEL, H., CARROLI, G., FARNOT, U., LUMBIGANON, P., BELIZÁN, J., BERGSJO, P., BAKKETEIG, L., LINDMARK, G. (2003) Womens' opinions on antenatal care in developing countries. Results of a study in Cuba, Thailand, Saudi Arabia and Argentina. *BMJ Public Health*, 3, 17.
- NORRIS, S.L., MOHER, D., REEVES, B.C., et al. (2013) Issues relating to selective reporting when including non-randomized studies in systematic reviews on the effects of healthcare interventions. *Res Synth Methods.*, 4, 36-47.
- NORWEGIAN MEDICINES AGENCY. (2012) Guidelines on how to conduct pharmacoeconomic analyses. In force from 1st March 2012.
- NOYES, J., GOUGH, D., LEWIN, S., et al. (2013) A research and development agenda for systematic reviews that ask complex questions about complex interventions. *J Clin Epidemiol*, 66, 1262-70.
- NUTBEAM, D. (2001) How does evidence influence public health policy? Tackling health inequalities in England. *Health Promot J Aust*, 14:154-158.
- OFFICE OF TECHNOLOGY ASSESSMENT (OTA) (1976) Development of Medical Technology: Opportunities for Assessment. Washington: Congress of the United States.

- OFFICE OF TECHNOLOGY ASSESSMENT (OTA) (1982) Development of Medical Technology: Opportunities for Assessment. Washington: Congress of the United States.
- OGILVIE, D., EGAN, M., HAMILTON, V., et al. (2005) Systematic reviews of health effects of social interventions: 2. Best available evidence: how low should you go? *J Epidemiol Community Health*, 59, 886-892.
- OGILVIE, D., FAYTER, D., PETTICREW, M., et al. (2008) The harvest plot; a method for synthesising evidence about the differential effects of interventions. *BMC Med Res Methodol*, 8, 8.
- O'NEIL, M., BERKMAN, N., HARTLING, L, et al. (2014) Observational Evidence and Strength of Evidence Domains: Case Examples. Research White Paper. (Prepared by the AHRQ Scientific Resource Center under Contract No. 290-2012-00004-C). AHRQ Publication No. 14-EHC001-EF. Rockville, MD: Agency for Healthcare Research and Quality.
- PAWSON, R. (2006). Evidence based policy: a realist perspective. London: Sage.
- PAWSON, R., GREENHALGH, T., HARVEY, G., WALSHE, K. (2005) Realist review - a new method of systematic review designed for complex policy interventions. *Journal of Health Services Research & Policy*, 10, 21-34.
- PETTICREW, M., ANDERSON, L., ELDER, R., GRIMSHAW, J., HOPKINS, D., HAHN, R., WELCH, V. (2013) Complex technologies and their implications for systematic reviews: a pragmatic approach. *J Clin Epidemiol*, 66, 1209-1214.
- PETTICREW, M., REHFUESS, E.A., NOYES, J. et al. (2013) Synthesising evidence on complex interventions: how meta-analytic, qualitative, and mixed-method approaches can contribute. *J Clin Epidemiol*, 66,1230-1243.
- PFADENHAUER, L.M., BURNS, J., ROHWER, A., REHFUESS, E.A. (2014) A Protocol for a systematic review of the effectiveness of interventions to reduce exposure to lead through consumer products and drinking water. *Systematic Reviews*, 3:36.
- PFADENHAUER, L., ROHWER, A., BURNS, J., BOOTH, A., LYSDAHL, K.B., HOFMANN, B., GERHARDUS, A., MOZYGEMBA, K., TUMMERS, M., WAHLSTER, R., REHFUESS, E. (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]. Available from: <http://www.integrate-hta.eu/downloads/>
- PIGOTT T, SHEPPERD S. (2013) Identifying, documenting, and examining heterogeneity in systematic reviews of complex interventions. *J Clin Epidemiol*, 66, 1244-50.
- PITT, M., MONKS, T., ALLEN, M. (2015). Systems modelling for improving healthcare. In: RICHARDS DA, INGALILL RH (eds.). *Complex interventions in health: an overview of research methods*. Routledge, Oxon.
- PIZZO, E., DOYLE, C., MATTHEWS, R., BARLOW, J. (2014) Patient and public involvement: how much do we spend and what are the benefits? *Health Expect*.
- POTTER, B. K., AVARD, D., ENTWISTLE, V.,KENNEDY, C., CHAKRABORTY, P., MCGUIRE, M. WILSON, B. J. (2009) Ethical, Legal, and Social Issues in Health Technology Assessment for Prenatal/Preconceptional and Newborn Screening: A Workshop Report. *Public Health Genomics*, 12:4, 4-10.
- POTTER, B. K., AVARD, D., GRAHAM, I. D., ENTWISTLE, V. A., CAULFIELD, T. A., CHAKRABORTY, P., WILSON, B. J. (2008) Guidance for considering ethical, legal, and social issues in health technology assessment: application to genetic screening. *Int J Technol Assess Health Care*, 24(4), 412-422.
- RAUDENBUSH, S., BRYK, A. (2002) Hierarchical linear models: applications and data analysis methods. 2nd ed. Thousand Oaks, CA: Sage Publications Inc.
- REUZEL, R. (2004) Interactive technology assessment of paediatric cochlear implantation. *Poiesis & Praxis*, 2, 119-137.
- REUZEL, R. P., VAN DER WILT, G. J., TEN HAVE, H. A., DE VRIES ROBBE, P. F. (1999) Reducing normative bias in health technology assessment: interactive evaluation and casuistry. *Medicine, Health Care, and Philosophy*, 2, 255-263.
- REUZEL, R. P., VAN DER WILT, G. J., TEN HAVE, H. A., DE VRIES ROBBE, P. F. (2001) Interactive technology assessment and wide reflective equilibrium. *J Med Philos*, 26, 245-61.

- REEVES, B.C., HIGGINS, J.P.T., RAMSAY, C., et al. (2013) An introduction to methodological issues when including non-randomised studies in systematic reviews on the effects of interventions. *Res Synth Methods*, 4, 1-11.
- RING, N.A., JEPSON, R., RITCHIE, K. (2011a) Methods of synthesizing qualitative research studies for health technology assessment. *Int J Technol Assess Health Care*, 27, 384-390.
- RING, N.A., RITCHIE, K., MANDAVA, L., JEPSON, R. (2011b) A guide to synthesising qualitative research for researchers undertaking health technology assessments and systematic reviews. NHS Quality Improvement Scotland (NHS QIS)
- RIP, A., MISA, T., SCHOT, J. (1995) Constructive Technology Assessment: A new paradigm for managing technology in society. In: RIP, A., MISA, T., SCHOT, J. (eds.). *Managing technology in society. The approach of Constructive Technology Assessment*. London and New York: Pinter Publishers.
- ROBERTS, M., RUSSELL, L., PALTIEL, D., CHAMBERS, M., MCEWAN, P., KRAHN, M. (2012) Conceptual Modeling: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force – 2. *Medical Decision Making*, 32, 678-689.
- ROBINSON, S. (2011). *A Framework for Simulation Conceptual Modeling*. Conceptual Modeling for Discrete-Event Simulation. Florida, US., Taylor and Francis Group.
- ROCKERS, P.C., FEIGL, A.B., ROTTINGEN, J.A., et al. (2012) Study-design selection criteria in systematic reviews of effectiveness of health systems interventions and reforms: A meta-review. *Health Policy*, 104, 206-214.
- ROHWER, A., BOOTH, A., PFADENHAUER, L., BRERETON, L., GERHARDUS, A., MOZYGEMBA, K., OORTWIJN, W., TUMMERS, M., VAN DER WILT, G. J., REHFUESS, E. (2016) Guidance on the use of logic models in health technology assessments of complex interventions [Online]. Available from: <http://www.integrate-hta.eu/downloads/>
- ROSENHEAD, J., MINGERS, J. (2009) *Rational analysis for a problematic world revisited. Problem structuring methods for complexity, uncertainty and conflict*, (2 ed.). John Wiley & Sons Ltd.
- RYAN, M., SCOTT, D., REEVES, C., BATE, A., VAN TEIJLINGEN, E. (2001) Eliciting public preferences for healthcare: a systematic review of techniques. *Health Technology Assessment*, 5, 186.
- SAARNI, S. I., ANTTILA, H., SAARNI, S. E., MUSTAJOKI, P., KOIVUKANGAS, V., IKONEN, T. S., MALMIVAARA, A. (2011) Ethical issues of obesity surgery--a health technology assessment. *Obes Surg*, 21, 1469-1476.
- SAARNI, S. I., HOFMANN, B., LAMPE, K., LUHMANN, D., MAKELA, M., VELASCO-GARRIDO, M., AUTTI-RAMO, I. (2008) Ethical analysis to improve decision-making on health technologies. *Bulletin of the World Health Organization*, 86, 617-623.
- SABATIER, P.A. (2007) *Theories of the Policy Process*. Westview Press.
- SACCHINI, D., CRAXÌ, L., REFOLO, P., MINACORI, R., CICHETTI, A., GASBARRINI, A., SPAGNOLO, A. G. (2014) Ethical assessment of hepatitis C virus treatment: the lesson from first generation protease inhibitors. *Digestive and Liver Disease*.
- SACCHINI, D., VIRDIS, A., REFOLO, P., PENNACCHINI, M., DE PAULA, I. C. (2009) Health technology assessment (HTA): ethical aspects. *Medicine, Health Care, and Philosophy*, 12, 453-457.
- SACKMAN, H. (1974) Delphi Assessment: Expert Opinion, Forecasting and Group Process. In: BROWN, T. (ed.). *An Experiment in Probabilistic Forecasting*. Santa Monica: Rand.
- SAINI, M., SHLONSKY, A. (2012) *Systematic synthesis of qualitative research*. Oxford: Oxford University Press.
- SAMBUC, C., THEBAUT, C. (eds.) (2013) *Methodological guide. Assessment of ethical aspects*. France: Haute Autorite de Sante.
- SANDMAN, L., HEINTZ, E. (2014) Assessment vs. appraisal of ethical aspects of health technology assessment: can the distinction be upheld? *GMS Health Technol Assess*, 10, Doc05.
- SBU. (2014) *Utvärdering av metoder i hälso- og sjukvården, en handbok. Etiska och sociala aspekter*. Stockholm: Statens beredning för medicinsk utvärdering.

- SCHÜNEMANN, H.J., TUGWELL, P., REEVES, B.C., et al. (2013) Non-randomized studies as a source of complementary, sequential or replacement evidence for randomized controlled trials in systematic reviews on the effects of interventions. *Res Synth Methods*, 4, 49-62.
- SCHWARZ, M., THOMPSON, M. (1990) *Divided we stand. Redefining politics, technology and social choice*. Philadelphia: University of Pennsylvania Press.
- SEE, C.W., SRINIVASAN, M., SARAVANNAN, S., et al. (2012) Prior elicitation and Bayesian analysis of the Steroids for Corneal Ulcers Trial. *Ophthalmic Epidemiol*, 19, 407-13.
- SGRECCIA, E. (2012) *Personalist Bioethics*. Philadelphia (US): NCBC.
- SHIELL, A., HAWES, P., GOLD, L. (2008) Complex interventions or complex systems? Implications for health economic evaluation. *BMJ*, 336, 1281-1283.
- SHRIER, I. (2011) Structural Approach to Bias in Meta-analyses. *Res Synth Methods*, 2, 223-37.
- SIEBERS, P.O., MACAL, C.M., GARNETT, J., BUXTON, D., PIDD, M. (2010) Discrete-event simulation is dead, long live agent-based simulation! *Journal of Simulation*, 4, 204-210.
- SNILSTVEIT, B., OLIVER, S., VOJTKOVA, M. (2012) Narrative approaches to systematic review and synthesis of evidence for international development policy and practice. *Journal of Development Effectiveness*, 4, 409-429.
- SQUIRES, H. (2014). *A methodological framework for developing the structure of Public Health economic models*. University of Sheffield.
- SQUIRES, J.E., VALENTINE, J.C., GRIMSHAW, J.M. (2013) Systematic reviews of complex interventions: framing the review question. *J Clin Epidemiol*, 66, 1215-22.
- STIRLING, A. (2008) "Opening up" and "closing down". Power, participation, and pluralism in the social appraisal of technology. *Science, Technology, & Human Values*, 33, 262-294.
- STRAUSS, A.L., CORBIN, J.C. (1990) *Basics of Qualitative Research: Grounded Theory Procedures and Techniques*. Sage Publications.
- STRECH, D., MERTZ, M., KNUPPEL, H., NEITZKE, G., SCHMIDHUBER, M. (2013) The full spectrum of ethical issues in dementia care: systematic qualitative review. *British Journal of Psychiatry*, 202, 400-406.
- STRECH, D., SOFAER, N. (2012). How to write a systematic review of reasons. *Journal of Medical Ethics*, 38, 121-126.
- SUTTON, A., ABRAMS, K. (2001) Bayesian methods in meta-analysis and evidence synthesis. *Stat Methods Med Res*, 10, 277-303.
- TAPPENDEN, P., CHILCOTT, J., BRENNAN, A., SQUIRES, H., STEVENSON, M. (2012) Whole disease modelling to inform resource allocation decisions in cancer: A methodological framework. *Value in Health*, 15:1127-1136.
- TASK FORCE FOR THE PREPARATION OF GUIDELINES FOR HEALTH TECHNOLOGY ASSESSMENT. (2009) Guidelines for conducting Health Technology Assessment (HTA) Version 2.1. Agency for Health Technology Assessment, Warsaw, April 2009. [Online]. Available from: www.aotm.gov.pl
- TA-SWISS, Z.F.T.-A. (2001) *Psychosoziale aspekte der ultraschall-untersuchung in der schwangerschaft. Studie des zentrums für technologiefolgen-abschätzung*. TA SWISS TAPPENDEN, P. (2011). *A methodological framework for developing Whole Disease Models: an application in colorectal cancer*. PhD thesis University of Sheffield.
- TELEMEDICINE, M. N. C. F. I. C. A. (2010) *MethoTelemed. Methodology to assess telemedicine applications*.
- THOMPSON, M., ELLIS, R., WILDAVSKY, A. (1990) *Cultural Theory*. Boulder: Westview Press.
- THOMPSON, S., EKELUND, U., JEBB, S., et al. (2011) A proposed method of bias adjustment for meta-analyses of published observational studies. *Int J Epidemiol*, 40, 765.
- THOMPSON, S., HIGGINS, J. (2002) How should meta-regression analyses be undertaken and interpreted? *Stat Med*, 21, 1559-73.

- TURLEY, R., SAITH, R., BHAN, N., REHFUESS, E., CARTER, B. (2013) Slumupgrading strategies involving physical environment and infrastructure interventions and their effects on health and socio-economic outcomes. Cochrane Database of Systematic Reviews (Issue 1).
- TURNER, R.M., SPIEGELHALTER, D.J., SMITH, G.C.S., THOMPSON, S.G. (2009) Bias modelling in evidence synthesis. *J R Stat Soc Ser A Stat Soc*, 172, 21–47.
- VALENTINE, J.C., THOMPSON, S.G. (2012) Issues relating to confounding and meta-analysis when including non-randomized studies in systematic reviews on the effects of interventions. *Res Synth Methods*, 6, 26–35.
- VAN HOORN, R., VAN DER WILT, G.J., TUMMERS, M., KIEVIT, W. (2016) Guidance on the integration of moderators of and patient preferences for treatment outcomes. In: VAN HOORN, R., TUMMERS, M., KIEVIT, W., VAN DER WILT, G.J. (eds.). *Guidance for the assessment of treatment moderation and patients' preferences* [Online]. Available from: <http://www.integrate-hta.eu/downloads/>
- VOSS, P.H., REHFUESS, E.A. (2013) Quality appraisal in systematic reviews of public health interventions: an empirical study on the impact of choice of tool on meta-analysis. *J Epidemiol Community Health*, 67, 98–104.
- WAHLSTER, P., BRERETON, L., BURNS, J., HOFMANN, B., MOZYGEMBA, K., OORTWIJN, W., PFADENHAUER, L., POLUS, S., REHFUESS, E., SCHILLING, I., VAN HOORN, R., VAN DER WILT, G.J., BALTUSSEN, R., GERHARDUS, A. (2016) Guidance on the integrated assessment of complex health technologies – The INTEGRATE-HTA Model [Online]. Available from: <http://www.integrate-hta.eu/downloads/>
- WELLS, G.A., SHEA, B., HIGGINS, J.P.T., et al. (2013) Checklists of methodological issues for review authors to consider when including non-randomized studies in systematic reviews. *Res Synth Methods*, 4, 63–77.
- WELLS, M., WILLIAMS, B., TREWEEK, S., et al. (2012) Intervention description is not enough: evidence from an in-depth multiple case study on the untold role and impact of context in randomised controlled trials of seven complex interventions. *Trials*, 28, 13–95.
- WELTON, N., CALDWELL, D., ADAMOPOULOS, E., VEDHARA, K. (2009) Mixed treatment comparison meta-analysis of complex interventions: psychological interventions in coronary heart disease. *Am J Epidemiol*, 169, 1158–65.
- WIDRIG, D., TAG, B. (2014). HTA and its Legal aspects: A Framework for Identifying Legal aspects in Health Technology Assessment. *Int J Technol Assess Health Care*, 30:6, 587–594.
- WILLIAMS, T., MAY, C., MAIR, F., MORT, M., GASK, L. (2003) Normative models of health technology assessment and the social production of evidence about telehealth care. *Health Policy*, 64, 39–54.
- WOERTMAN, W., VERMEULEN, B., GROENEWOUD, H., VAN DER WILT, G.J. (2013) Evidence based policy decisions through a Bayesian approach: the case of a statin appraisal in The Netherlands. *Health Policy*, 112, 234–40.
- WORLD HEALTH ORGANISATION (WHO). (2015) Health technology assessment. [Online]. Available from: http://www.who.int/medical_devices/assessment/en/ [Accessed: 23.10.2015].
- WIDRIG, D., TAG, B. (2014) HTA and its Legal aspects: A Framework for Identifying Legal aspects in Health Technology Assessment, *Int J Technol Assess Health Care*, 30, 587–594.
- WYNNE, B. (1995) Technology assessment and reflexive social learning: observations from the risk field. In: RIP, A., MISA, T., SCHOT, J. (eds.). *Managing technology in society. The approach of Constructive Technology Assessment*. London and New York: Pinter Publishers.
- YAFFE, J., MONTGOMERY, P., HOPEWELL, S., SHEPARD, L.S. (2012) Empty Reviews: A Description and Consideration of Cochrane Systematic Reviews with No Included Studies. *Plos One*, 7, e36626.

9 APPENDIX

9.1 APPENDIX OF THE ASSESSMENT OF ECONOMIC ASPECTS IN HTA

9.1.1 Review of existing guidance on economic evaluation within HTA

The distinguishing feature of HTA and health economics within HTA, is its focus on using evidence to support healthcare decision / policy making. The review of health economic guidance therefore focuses on guidance pertaining within the EU and issued by or relating to national policy making bodies. The review takes a specific focus on countries directly involved in the INTEGRATE-HTA project namely, Norway (Norwegian Medicines Agency 2012), Italy (Capri 2001), Germany (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, 2009), Netherlands (College voor zorgverzekeringen, 2006), Poland (Task force for the preparation of guidelines for health technology assessment, 2009) and England (NICE, 2009; NICE, 2013). Guidance current in 2013 was included in the review.

The review is divided into four themes coherent with the key economic elements within HTA described by the HTA Core Model:

- ▶ theoretical underpinning, health economics methodology and perspective,
- ▶ scoping and defining the decision problem,
- ▶ health and wellbeing outcomes and
- ▶ resources and costs.

Discussion relating to the four themes within the guidance was extracted and data extraction tables for each theme are available from the authors. A narrative critique of the guidance with respect to the aspects of complexity defined by the project and with reference to the complexity science literature. Recommendations for practice and recommendations for future research are identified. Recommendations for practice are expanded on within the guidance in Chapter 3.

9.1.2 Theoretical underpinning, health economics methodology and perspective.

Review of existing guidance

Health technology assessment is concerned with providing evidence to support effective resource allocation decision making by health care decision makers. Therefore the different national decision making contexts have a defining influence on the local requirements for economic evaluation within HTA.

Thus for example in Germany the Institute for Quality and Efficiency in Healthcare (IQWiG) provides support to the Federal Joint Committee (G-BA) and the National Association of Health Insurance Funds (GKV-Spitzenverband) with the objective of contributing to the continuous improvement in quality and efficiency of health care. IQWiG, an independent scientific institute, provides support through undertaking reviews of the evidence on the clinical and economic impact of interventions. The assessment of the relation of benefits to costs, or economic assessment, is used by the GKV-Spitzenverband in setting the appropriate maximum reimbursable price of medications on behalf of the Statutory Health Insurance (SHI) insurants (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, 2009).

In the Netherlands guidelines for pharmacoeconomic research are issued by the College voor zorgverzekeringen (Health Care Insurance Board) (College voor zorgverzekeringen, 2006). These guidelines are used as an assessment framework when evaluating reimbursement files submitted by manufacturers in application for novel technologies to be included in the Drug Reimbursement System (GVS) listings and in respect of pharmaceutical prescribing controls.

In England and Wales the National Institute for Health and Care Excellence (NICE) provides advice to the NHS across a broad spectrum of domains including clinical guidelines for whole disease areas, guidance on the use of specific technologies and public health guidance. By and large the NICE Technology Appraisals programme tends to assess submissions of evidence made to NICE by technology manufacturers, whilst the NICE Public Health programme tends to commission independent reviews of the evidence from third party institutions including the academic sector (NICE, 2009; NICE, 2013).

In all but one of the cases considered the decisions that analysis is seeking to inform relate solely to the use of a technology either as a simple use/don't use reimbursement decision as in the Netherlands and Norway or within a reimbursement and price setting

framework as in Germany and Italy, with the NICE Technology Appraisals programme having consulted over a move from the former to the latter. The exception to this is the NICE Public Health programme where guidance explicitly may address a wide range of topics and issues, and usually does more than just make recommendations about effective and cost-effective interventions. As well as 'what works', it often addresses when, why, how, and for whom an approach does (and does not) work.

In all countries decision making regarding the use of medicines is made in the context of statutory licensing frameworks that govern the use of products in the health market place, in the EU this is either through the unified European Medicines Agency (EMA) process or through country specific licensing bodies such as the Norwegian Medicines Agency. The economic decision making criteria in all countries focus primarily on health benefits and the relationship of costs to benefits of a decision. In Germany an assessment of benefit is first made and only beneficial technologies are submitted to an economic assessment that compares the novel technology with existing technologies in the same therapeutic area. The incompleteness of the Efficiency Frontier approach is recognised by the authors and thus cost effectiveness information is stated to be used alongside budget impact analyses and other unspecified information. Similarly the Dutch and Norwegian institutions are not explicit about the broader criteria used alongside cost utility information provided by economic analyses. In Italy cost effectiveness information is explicit in using alongside international drug pricing information, budget impact analyses and other pharmaceutical commitments relevant to the national economy. In England and Wales, NICE is explicit in using cost effectiveness alongside clinical effectiveness, non-health factors including social value judgements and broader impacts beyond health and social care. For technology appraisals non-health criteria are evaluated in terms of willingness to forego health benefits, whereas within public health there is recognition of the need to explicitly identify and assess these broader criteria.

All decision making bodies recognise that economic evaluation cannot be considered as a self-contained decision making system and that no approach can provide 'criteria for absolute rationality'. Economic evidence is therefore considered within frameworks for decision making that recognise political and administrative theories and processes.

With regard to economic perspective the Dutch and Norwegian institutions advocate a societal perspective for the economic evaluation of healthcare interventions. In Germany, IQWiG defines the default perspective as the 'SHI insurants', that is people in receipt of statutory health insurance, though other perspectives may be requested in specific circumstances. In Italy the joint societal and Italian National Health Service perspective is defined. In England and Wales the perspective for technology appraisals is described as being health and social care, with the provision that a broader perspective may be directed by the Minister for Health in specific circumstances. In NICE public health guidance three levels of perspective are described, the prime perspective being described as 'public service'. Beyond this it is recognised that frequently a broader and potentially multi-perspective is required and relevant to decision making by different stakeholders, and thirdly the 'health and social care' perspective is relevant to enable a specific health focus and comparability to other health interventions.

The guidance documents recognise the following economic methods commonly referenced to Gold (Gold et al., 1996) and Drummond (Drummond et al., 2005):

- ▶ Cost Benefit Analysis (CBA), where the effects of an intervention are valued in monetary terms allowing an assessment of whether the net benefit is positive or negative.
- ▶ Cost-Effectiveness Analysis (CEA) which focuses on the ratio of costs to effects, with effects measured in terms of generic outcomes, such as life years gained, or disease specific outcomes.
- ▶ Cost Utility Analysis (CUA), a subset of CEA where effects are measured as a utility, commonly assumed to mean cost per quality adjusted life year gained.
- ▶ Cost-Minimization Analysis (CMA), where it is assumed or demonstrated that effects are identical or equivalent, so it is sufficient to consider the costs alone.
- ▶ Cost-Value Analysis (CVA), which is a form of CUA where the utility measure attempted is to capture a broader scope than the quality adjusted life year, specifically attempting to capture valuations concerning fairness and justice of allocations associated with competing programmes or interventions (Nord, 1999).
- ▶ the Efficiency Frontier approach, that is essentially a reformulation of the CEA approach (Caro, 2010).

- Cost Consequence Analysis (CCA), where comparative costs and consequences of interventions are simply itemised separately allowing decision makers to make a judgement about the relative merits of interventions.

The guidance documents from The Netherlands, Norway and England and Wales (Technology Appraisal) identify the preferred health economic method as being CUA where this is specifically taken to mean a cost per quality adjusted life year gained. In Italy Capri et al. state a somewhat broader preference for CEA including CUA. In Germany, IQWiG recommends the use of the Efficiency Frontier approach. The NICE public health programme states an increased importance for CCA and CBA, but retains a routine requirement for CUA, again meaning cost per QALY gained, in order to enable a specific health perspective analysis to be retained and to allow comparative assessment with a broader range of health interventions. CBA is generally not recommended, with guidance referring to the ethical and technical challenges associated with setting a monetary value on health improvements as the limiting factors. CMA is also not generally recommended due to difficulties in establishing true equivalence in effectiveness, though The Netherlands and Norway do make allowance for this type of analysis.

Only the guidance documents from The Netherlands and the England and Wales NICE public health programme are explicit in stating their theoretical or philosophical basis, with The Netherlands referring to welfarism as the basis for their economic guidance. In contrast, for Germany, Norway, Italy, NICE Technology Appraisals, and indeed The Netherlands, the methods and techniques included in the health economic guidance, specifically the approaches to outcome valuation, the perspective and the attachment to the cost per QALY gained method, imply an extra-welfare theoretical position. The NICE public health programme explicitly recognises the broad range of scientific evidence and research traditions that is relevant to public health including clinical medicine, epidemiology, health economics, medical sociology, health psychology, medical anthropology, nutrition, sports science, nursing, education, political science and health education and promotion. This diversity means that a single theoretical basis is not feasible or appropriate, rather a conceptual framework for guidance is made explicit. The conceptual framework is based on a number of principles. These are as follows. First, that there are determinants of health and disease which are much broader than, but include, bio-

medical causes. Second, these determinants operate in highly patterned ways which reflect inequalities in society. Third, the determinants work through causal pathways to disease. Fourth, the causal pathways help to identify ways of preventing and ameliorating disease. Fifth, there are also causal pathways for the promotion of health. Sixth, positive and negative causal pathways cross physical, biological, social and psychological boundaries.

Discussion

The health economics guidance and the supporting methodological literature frame the economic decision problem as one of maximising health outcomes from the expenditure of a fixed budget (Gold et al., 1996; Drummond et al., 2005). Thus health economics guidance is seen to arise from the need for regulation and control of expenditure in healthcare systems and focuses principally on reimbursement decisions for individual drugs and other state funding decisions such as reimbursement within statutory health insurance schemes. In these cases the decision problem is constructed as either a simple binary decision, do/don't reimburse, or its corollary, identifying an economically acceptable reimbursement price. Two points arise from this consideration. Firstly whilst HTA is identified as being potentially relevant to three decision making levels; the clinical patient/healthcare professional level (micro), the system administrative/management level (meso) and the health policy level (macro), the economic methods relate only to the policy level decision problem and indeed involve assumptions and simplifications that depend upon this policy level focus. Secondly, in so far as the key part of a pharmaceutical intervention is a single licensable component these interventions may be classed as simple rather than complex interventions (guidance from The Netherlands explicitly claims relevance of methods to the general field of healthcare, though this is not justified). Whereas public health interventions, for example involving behaviour change or risk factor modification, tend to fall into the class of complex interventions. It is therefore worth noting that guidance arising from public health recognises a broader range of questions, when, why, how, and for whom an approach may be economically attractive. This suggests that health economics for complex interventions is likely to have to respond to a broader range of questions than simple societal level only reimbursement decision.

The simple binary construction of the decision problem involves essentially two stakeholders or agencies,

the health or public service system and the technology manufacturers. The decision analytic approach assumes that decision making is being made within a stationary context, whether in considering reimbursement or pricing, and does not capture potentially dynamic relationships between the agents. This framing of the decision problem therefore avoids complexity associated with learning, adaptation and evolution. Whilst there has been some tentative implementation of Game Theory based applications in health economic pricing mechanisms (Johnston & Zeckhauser 2009) this is not generally taken up and is not reflected at all in the guidance considered. Similarly whilst Birch and Gafni identify potential limitations of the cost effectiveness approach (Birch & Gafni 2006) in achieving 'bigger bangs for the buck', their analysis focuses on the fallacy of the threshold and remains within the static system assumptions of standard health economic methodology. There is therefore potential for complexity methods to be used to investigate the impact of relaxing the stationarity assumptions inherent in current health economic methodology.

The comparison between decision making criteria suggests that the most well developed implementation of health economic methods occurs where decision making criteria are most transparently defined. This highlights that, whilst all decision making is recognised to occur within a political and administrative context, the implementation of health economic methods is associated with a shift towards administrative technical efficiency criteria over political process. In this movement the health economics academic sector plays a key role as arbiter of method (and accreditation of value judgements (Lessard 2007)) and as provider of independent advice to health care decision makers and technology manufacturers.

Current guidance focuses on system wide economic perspectives, either that of the public service, societal perspective or the health insurers'. The NICE public health guidance suggests that it may also be important, especially where complex interventions involve decision makers outside the immediate control of the health system, to understand and include the perspectives of stakeholders in the system. Economic guidance for complex interventions needs to enable multiple perspectives to be recognised.

In considering current health economic methods, where complex interventions are such that multiple perspectives are relevant, this implies an increased importance for CCA not as a substitute for the construction of a single decision making objective func-

tion, but rather to recognise the potentially differing information needs of different stakeholders/decision makers.

All of the current health economics guidance arises from an extra-welfarist theoretical position. Several of the strong assumptions underpinning this position, for example stationarity and equilibrium are relaxed by the complexity science approach. This echoes Arthur (Arthur, 2013) who places traditional theoretical methodologies as special cases of the broader complexity methodologies.

Shiell (Sheill et al, 2008) suggests that even where an intervention is complex, if its interaction with its setting is simple, then it may well be sufficient to treat the intervention as a black box when assessing its economic impact. Shiell recognises that in this case, standard methods may well be sufficient to inform decision making. Shiell identifies however, that if there is significant interaction between the intervention and the setting then traditional methods of assessing the economic and indeed the health effectiveness are subject to major problems. Shiell suggests that a possible response maybe to move towards a closer relationship between evaluation and practice. This has important implications including the necessity to collect economically relevant information as a part of practice evaluation and to ensure that economic criteria are relevant to micro and meso level decision making. At the macro or policy level economic evaluation may need to enable decision making regarding meta-interventions, for example structural interventions that impact on the development of the system, in addition to assessing the economic effectiveness of individual technologies. Bringing evaluation and decision making closer together may well be an appropriate response, but it does leave a question mark about the exact role of HTA in this context. Furthermore, there is currently no method for assessing whether the complexity in an intervention/setting matters.

The complexity science approach relies heavily on computation as a method for exploring the structure of a problem situation and for theory building. This is very different to traditional cost effectiveness methods that might use computational simulation for generating probabilistic predictions of key outcomes. In complexity science computation is used as a tool for understanding the rules that govern a system, for describing patterns of behaviour in the system and for exploring ways to intervene in a system to promote desired outcomes (Miller & Page 2007). This highlights that potentially the role for HTA in considering

complex systems is through a shift towards meta-interventions. That is rather than focusing on the cost effectiveness of individual technologies, focusing on structural interventions that impact on the development of the system. For example Arthur (Arthur, 2013) characterises a system as being defined by the set of technologies and needs that it comprises, with evolution of the system arising from recombination and development of novel technologies to meet unmet needs and give rise to new needs. Such a model would move health economics within HTA from a passive gate-keeping role, as implied by the yes/no reimbursement framework, to playing an active role in shaping the development and definition of technologies that comprise the health system.

NICE public health assessment recognises that a single theoretical base is insufficient for adequately assessing public health complex interventions. Rather a conceptual framework is proposed that describes determinants of health that operates through causal pathways to disease, and that understanding these causal pathways, across physical, biological, social and psychological boundaries, is the mechanism for identifying effective interventions. This conceptual framework has a strong resonance with the systems

approach described and promoted by the World Health Organisation, indeed it constitutes a specific public health application. (de Savigny & Adam 2009) In addition to exploring novel computational complexity approaches, a systems thinking approach may be useful for the assessment of complex interventions in complex setting.

9.1.3 Scoping and defining the economic decision problem

Review of existing guidance

The review focuses on two aspects of health economics guidance relating to scoping and defining the decision problem, firstly, the content of the scope/decision problem and secondly the process by which the scope/decision problem is defined. Once again the review takes a specific focus on countries directly involved in the INTEGRATE-HTA project.

Firstly guidance from Norway and the England and Wales NICE technology appraisals programme are explicit in using the Population, Intervention, Comparator, Outcome (PICO) framework taken from the systematic reviews domain as the basis for defining the content

Theoretical underpinning, health economics methodology and perspective.

Recommendations for research

Complex systems challenge the traditional role of HTA and specifically economic evaluation in HTA. Methodological development is required to further understand the potential of complexity science methods for changing the role of health economics within HTA in supporting health policy making.

The potential of computational complexity science methods to provide a health economic framework that allows the role of adaptation, evolution and strategy playing in the health economic market should be investigated.

Methods for assessing whether the complexity in an intervention/setting matters for economic evaluation are required.

Economic methods are required that respond to a broad range of decision problems, such as when, why, how, and for whom intervention may be appropriate.

Economic methods for complex interventions need to enable multiple perspectives to be recognised.

Recommendations for practice

A systems approach provides a useful conceptual framework for the assessment of complex interventions in complex setting.

In considering current health economic methods for complex interventions there is likely to be an increased role for cost consequence analysis (CCA) to support decision making in the presence of multiple perspectives.

of the economic decision problem. The guidance from Germany, Netherlands and Italy implies a similar use of this framework, with the discussion relating to the structure of the problem being once again focused around these issues. All guidance has some discussion regarding the relevant time horizon for analysis and is consistent in relating this to the ability to capture all the potential health and resource impacts of a novel intervention.

The NICE technology appraisals guidance explicitly differentiates between the scope of the appraisal and the description of the decision problem. In addition to the PICO the scope also describes the context of the decision problem, including information about the relevant disease or condition and describes the regulatory status of the technology and the Committee's rationale for developing guidance. The scope will also describe relevant stakeholders including professional and patient organisations and societies. An important role for the scope is to define the boundaries for assessing the evidence and for the committee's decision-making.

The NICE public health guidance describes four key documents associated with the scope/decision problem: a topic specific conceptual model, a logic model, a topic advisory workshop briefing document and finally a scope. The content of these documents and the process by which they are developed is not so easily disentangled and is therefore discussed below in more detail together with the description of process.

Topic selection and scoping is an iterative process whereby the generic conceptual framework for public health guidance is used as a basis for developing a topic specific conceptual framework, logic model and briefing document for a topic advisory workshop (TAW). The TAW produces a set of referrals for consideration by government health ministers. A scope is further developed for confirmed topics. The iterative process involves consultation with a progressively wider group of stakeholders. Firstly, suggestions for guidance are generated by an expert professional group. Secondly, the TAW involves the above professional group plus representation from a range of public, private and third sector organisations including relevant patient, carer and service user groups. Thirdly, this expanded group is invited to consult on the scope which is also opened to public consultation. Evidence is used throughout this process with preliminary information gathering exercises throughout.

The health economics guidance from The Netherlands, Norway and Italy does not describe in detail the process for developing the scope/decision problem description. In the Italian guidance there is reference to 'debate between the government and the companies' in selecting comparators for the intervention. In Norway it is stated that the assessment agency NOMA has the obligation of counselling applicants before and after the application is submitted, it is not explicit whether this includes counselling on the appropriate definition of the decision problem and/or methods. In Germany the IQWiG guidance describes the development of an influence diagram and a specification of the model. The influence diagram graphically represents the factors and possible associations that might have an influence on the research question(s) to be modelled. The model concept should illustrate how the health effects of the evaluated therapeutic options are linked to concrete health outcomes and resource use, and how they are projected over the time horizon of the model. In addition, the model concept should explain how interconnections in the influence diagram will be dealt with, providing justification for these choices and serving as the design plan for the model.

The topic specific conceptual framework describes the assumed relationships between action and outcomes including any relevant programme theory or theory of change (Pawson, 2006; Weiss 1995). Topics are mapped onto the vectors of causation outlined in the framework (population, environment, society and organisations) and cross-classified according to the potential level of intervention (population, community, organisation, family, domestic or individual). The framework is used to help define the key issues involved in a broad topic area and specify how defined topics fit into the overall strategic map of existing public health initiatives. The framework is also used to construct a logic model that encapsulates the assumed relationships between action and outcomes.

TAW briefing document aims to: map the topic onto the vectors of causation and levels of delivery, outline the systems involved in delivery, establish the importance of the topic and identify links to policy. This document identifies the links between the intervention and its health and other outcomes using a logic model, a programme theory or a theory of change, identifies any equity issues and discusses the resource implications of taking or not taking action.

The scope for guidance should: specify precisely which interventions or types of interventions are covered. This should cover the nature and content of each public health action, and the way it is delivered and describe the assumed causal mechanism, mediator or link between the action(s) and the outcome(s). This document describes the policy context including questions that the guidance will address, ensures the guidance can be developed in the allocated time and identifies the economic approach, including any additional perspectives that will be taken into account, such as employers or the private sector.

Discussion

The guidance from Germany, The Netherlands, Norway, Italy and NICE technology appraisals relate principally to technologies that are subject to reimbursement control and licensing. In Germany, Italy and The Netherlands reimbursement is restricted to technologies that have been through the assessment process, the prioritisation of topics is therefore straightforward. In contrast, the NICE public health guidance has a sophisticated process for analysing broad topic areas and identifying and prioritising specific (sets of) interventions for assessment.

The above guidances all use the PICO framework for specifying the decision problem, this framework derives from the systematic review methodology for specifying a well-defined research question. It should be noted that this is not necessarily synonymous with a well-defined decision problem. Where a technology is subject to licensing, it is by requirement well defined and stable, that its essential components are well understood and not liable to evolve and in so far as an indication is specified, a relevant population is implied. Given this is the prevailing context for the development of economic guidance it is perhaps no surprise that often little is said regarding the process of deriving a scope. This gap in methodology has recently been recognised by the ISPOR task force on good modelling practice, with a special focus on conceptual modelling (Roberts et al., 2012). Recent research on avoiding and identifying errors in models identified that without a broader understanding of a clinical decision problem it is not possible to make a judgment about how well a given PICO construction meets decision makers' requirements (Chilcott et al., 2010). The NICE technology appraisals guidance recognises this and gives separate consideration to the scope and the decision problem, which reflects the model development process described by Tappenden and Chilcott (Tappenden et al., 2012).

The NICE guidance for public health interventions devotes detailed attention to the process for developing the scope of an assessment (reflected in the balance of the description provided in the above review). As noted above the economics component of NICE public health guidance is descended from the NICE clinical guidelines programme and is not wholly coherent with the broader framework for public health assessment. Recent doctoral research undertaken at SCHARR (Squires 2014) has focused on developing the structure of economic models in public health that addresses this issue. This modelling framework deals explicitly with understanding the decision problem, defining the scope of the economic assessment and deriving a model of the fundamental interactions within the problem. The framework is based upon four key principles: (1) a systems approach to Public Health modelling should be taken; (2) developing a thorough documented understanding of the problem is imperative prior to and alongside developing and justifying the model structure; (3) strong communication with stakeholders and members of the team throughout model development is essential; and (4) a systematic consideration of the determinants of health is central to identifying all key impacts of the interventions within Public Health economic modelling.

The process defined by Squires and outlined in Figure 14 below is proposed as a basis for translation to the broader complex interventions case, through considering how this framework responds to the aspects of complexity. The starting point for the framework is a consideration of the multiplicity of stakeholders and decision making perspectives pertinent to the decision problem, this aspect of the framework roots it firmly in the consideration of complex interventions in complex settings. The systematic approach to defining potential causal pathways within the system, including positive and negative feedback, meets the requirement for considering the nature of interactions within the system. However, it is less clear how well the framework captures the potential for adaptive behaviour within a system, the potential for co-evolution of an intervention and its setting, or indeed the impact of historicity and path dependence. Indeed, this potential weakness is recognised in the research and underlies the recommendation to undertake further research to explore the potential of computational methods in complexity such as agent based modelling, social network analysis and the modelling of behaviour in the health economics field.

Scoping and defining the decision problem

Recommendations for research

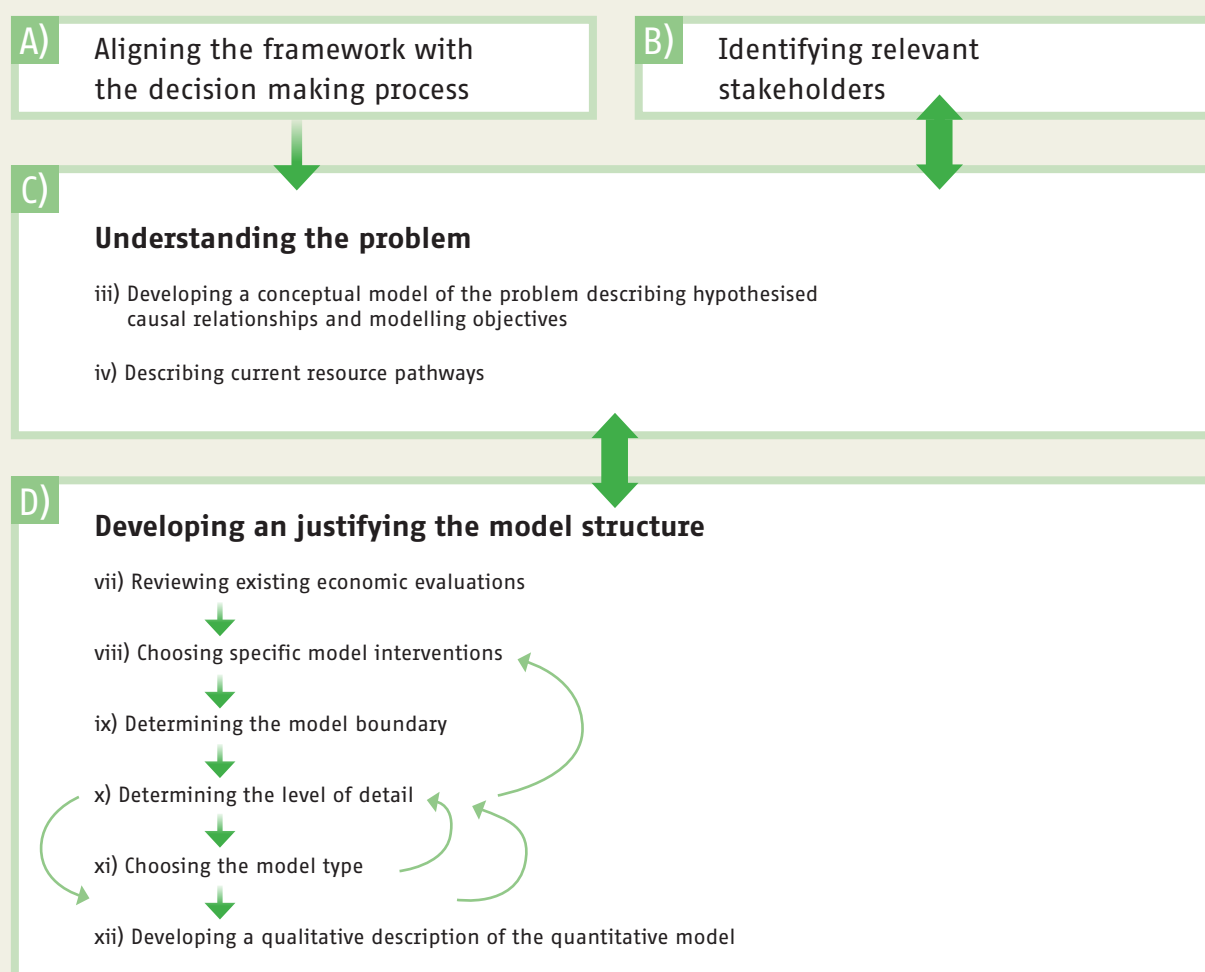
Research into the use of computational modelling techniques, such as agent based modelling and social network analysis for understanding the health economic impact of adaptive behaviour and co-evolutions of intervention and setting within HTA is required.

Further research into the modelling of behaviour within health economic models of complex interventions in complex settings is required.

Recommendations for practice

An explicit process for identifying and prioritising research questions and defining the scope of assessment is an important component of a health economic analysis of interventions within complex systems. It is proposed that an iterative, consultative approach is used.

Figure 13: Overview of conceptual modelling framework for economic modelling of complex interventions (After Squires).



9.1.4 Health and wellbeing outcomes

Review of existing guidance

Current health economics guidance for HTA across Europe typically focuses on health outcomes. For instance, in England and Wales the NICE Reference Case indicates that all direct health effects should be considered, whether for patients or, when relevant, carers (NICE, 2013). Current guidelines from other European countries, including Italy, Netherlands, Poland and Norway have a similar focus. Within the guidelines studied there is only one example where the guidelines go beyond this specific focus on health effects; the NICE Public Health (PH) guidance explicitly states that other broader effects will be considered in some circumstances. Specifically, for local government guidance, non-health benefits “may also be considered, where appropriate”. However, the inclusion of such effects will only be considered on a “case-by-case basis” (NICE, 2009).

The chosen perspective for the analysis will influence the outcomes to be considered. A societal perspective, as advocated by some countries, including The Netherlands and Norway, takes into account the full range of outcomes, including benefits that may accrue to family members, carers, or to society in general (including through increases in economic productivity) (College voor zorgverzekeringen (2006), Norwegian Medicines Agency (2012)). Countries which adopt a more narrowly focused perspective as the primary analysis (e.g. in England and Wales the perspective for the NICE Reference Case is the NHS and PSS and in Germany the default perspective is defined as the SHI insureds'), may also allow other perspectives to be considered in specific circumstances. The Italian guidance requests both a societal and Italian Health service perspective (Capri et al., 2001). The NICE PH guidance takes a primary ‘public service’ perspective, but also acknowledges the need for a broader and potentially multiple-perspective, relevant to decision making by different stakeholders (NICE, 2009). In addition it is acknowledged that a health and social care perspective may be relevant where there is a need for a specific health focus and also where comparability to other health interventions is important.

In terms of measurement of health benefit, the QALY is the most commonly recommended measure. Where explicitly stated within guidance, the use of the QALY has been advocated on the basis that it allows comparison across different diseases, allows inclusion

of both the impact on interventions on survival and on quality of life and supports elicitation of preferences for health states (Norwegian Medicines Agency, 2012). Shortcomings of the QALY are however widely acknowledged. (Value in Health Special Issue : Moving the QALY forward) The Norway guidelines, in addition to recommending the QALY, also recognise cost-value analysis, whereby health gains are valued dependent on baseline health severity, with improvements from a severe baseline health having greater societal value than similar improvements from better baseline health states (Norwegian Medicines Agency (2012)). In Germany, the HTA approach does not require priority setting within the global health care system and they tend to use a narrower definition of health than EQ-5D. Given that there is no imperative for a universal measure of benefit and a range of measures are considered acceptable including clinical measures, responder measures or aggregate measures (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG), 2009). In England and Wales the NICE PH requires both cost effectiveness analysis (CEA) and cost utility analysis (CUA) to be considered routinely, but in addition there is increasing emphasis on cost-consequences analysis (CCA) and cost-benefit analysis (CBA). This is partly on the grounds that local government is largely responsible for implementing public health programmes, and is responsible not only for the health of individuals and communities, but also for their overall welfare (NICE, 2009). This approach also aims to take into account the fact that Public Health is less centralised than the NHS. The Polish guidelines support the use of CCA, alongside CEA or CUA as part of a standard economic analysis (Task force for the preparation of guidelines for health technology assessment, 2009).

Approaches to the valuation of health benefits also differ between countries. In England and Wales, the NICE Reference case is very specific and states that health-related quality of life, or changes in health-related quality of life (HRQoL) should be measured directly by patients and that valuation of HRQoL should be based on a valuation of public preferences from a representative sample of the UK population using a choice-based method. The EQ-5D is specifically recommended, to avoid the issue raised by different methods of measuring HRQoL leading to different results. (NICE, 2013) It is however feasible to make a case for other measures to be used in situations where the EQ-5D can be demonstrated to be inappropriate. Conditions where EQ-5D has been found to be inappropriate include people with mental health pro-

blems (Brazier et al, 2014), along with some vision disorders and hearing (Longworth et al., 2014). Other countries are less specific, for instance Norway only specifies that the QALY outcomes are to be calculated using multi-attribute utility (MAU)-instruments that evaluate both the physical and psychological condition of the patient as well as his/her social functioning (Norwegian Medicines Agency (2012)). This includes EQ-5D along with Short form (SF) 6D and 15D. In Italy the use of a disease specific instrument, a general instrument (such as SF-36), alongside an instrument for surveying preferences e.g. Health Utility Index (HUI) or EQ-5D is recommended (Capri et al., 2001).

Discussion

Current HTA guidances typically do not make reference to complexity. Complex interventions, and particularly those operating within complex systems, interact with the context and setting of the health system within which they act and this raises additional challenges in relation to outcomes for HTA. To date there has been limited acknowledgement within European guidances of how the issues of complexity in HTA may influence outcomes assessment.

► **Health and non-health outcomes**

Health care decision-making to date has typically focused on improvements in health and this has translated into the recommended use of the QALY within cost utility analysis (CUA). This is most appropriate when the main or only benefit is a health benefit. It should be noted that although EQ-5D is limited to health in the descriptive system this does not mean the index it produces is limited to health. This is because the health state valuation task asks respondents to consider the impact of health on their lives (i.e. respondents are giving up life years) but using EQ means only benefits that come via health (e.g. poor self care reduces dignity) are taken into account; however the treatment may also impact on dignity separately.

The benefits of interventions that seek to improve an individual's quality of life beyond health may not be adequately reflected within current HTA processes. For example, in the PH field there has been growing recognition that the objectives of many complex interventions are broader aspects of quality of life. These include non-health outcomes such as empowerment, participation, the ability to form or maintain friendships, feel safe or retain dignity and self-respect, rather than health per se (Kelly, McDaid, Ludbrook &

Powell, 2005 in Coast et al.). In such circumstances the use of existing tools such as the EQ-5D to derive QALYs may fail to take account of the full benefits and therefore the interventions under consideration may be at a disadvantage compared with standard health care interventions when evaluated under current processes (Lorgelly et al.). Annemans et al. raised this issue in relation to the value of a complex health technology such as personalised medicine, describing the issue in terms of process utility. Process utility relates to the satisfaction derived from the process of using a technology rather than the actual outcomes. For diagnostic tests some of the benefit may be in the value associated with finding out about the result and obtaining advice, even if this does not result in a change in treatment strategy. However these benefits cannot currently be measured and therefore cannot yet be explicitly taken into account in decision making (Annemans et al., 2013).

In the field of palliative care, it has been suggested that end of life care (EoLC) may often be seeking to provide good quality care rather than health improvement and that EoLC may have more in common with interventions traditionally provided through social services (Sutton et al., 2014). In addition the quality of dying may differ from the quality of life. Some efforts to conceptualise this quality of dying have identified important domains for a 'good death', such as personal autonomy (the ability of the person to make his or her own decisions, which forms the basis of informed consent and shared decision making), maintaining dignity, providing support and enabling preparation for death, which are not captured by existing HRQoL instruments. It has therefore been suggested that failing to consider benefits beyond health in decision-making in palliative care may disadvantage palliative care interventions under current processes. (Sutton et al., 2014; Round, 2014).

Existing measures such as EQ-5D may not be adequate to reflect measures beyond health and therefore may not cover all outcomes considered to be important to decision makers. Alternative measures exist in other sectors, such as the Adult Social Care Outcome Tool (ASCOT) in social care and the preference-weighted ICECAP capability index, measures of wellbeing such as the Warwick-Edinburgh Mental Well-Being Scale (WEMWBS) and the ONS-4 in public health. The potential use of multiple outcome measures raises the issue of how to combine them in decision making and in particular, how to use such measures in situations when measurement across sectors is required. A recent re-

view aimed at stimulating research in this area, outlined a range of alternatives for addressing this issue, which fall into three broad categories: extending the QALY beyond health, using wellbeing to value outcomes and using money to value outcomes (Brazier & Tsuchiya, 2015).

Methodological development in measuring and valuing health and non-health outcomes is an on-going agenda both in terms of expanding the domains of outcomes included and developing the methods of assessment. Much of the research agenda is related to the underlying complexity of interventions and the systems within which they act and is directly relevant to economic evaluation in HTA. One of the challenges in seeking to take account of a broader range of outcomes relates to the indeterminacy in outcomes definition. It is not clear that there is a fixed domain of outcomes which will be appropriate for all complex interventions. If a fixed domain of outcomes does not exist the question of how to value and synthesise varying outcomes for different interventions remains and achieving a transparent and coherent decision making process still presents challenge

► Multiple outcomes and perspectives

The MRC definition of complex interventions outlines a number of potential dimensions of complexity, one of which is the number and variability of outcomes (Craig et al., 2008). Where complexity is evident there is likely to be a range of outcomes which are potentially relevant.

Typically the main focus in HTA is on patient outcomes. The NICE Reference Case indicates that all direct health effects should be considered, whether for patients or, when relevant, carers (NICE, 2013). Outcomes of other agents may be particularly important in certain cases, for instance carers in the context of palliative care or families in the context of children's health. In palliative care the outcomes of both patients and carers may be influenced by the same intervention. Whilst much research in these areas exists, there is no consensus on an overarching conceptual model for identifying and incorporating wider intervention effects (Samuel et al., 2012). These difficulties are exacerbated by the presence of potentially non-linear relationships between care recipient physical, behavioural and other impacts and carer/parent quality of life meaning that effects are disease/condition specific and difficult to generalise (Turnbull et al., 2007). Furthermore there is limited guidance on how to combine impacts on multiple people if different measures are used, in

terms of who benefits, how you measure the benefits to them and how to combine the benefits in order to facilitate economic analysis.

Outcomes throughout the health care system will need to be explored and taken into consideration, as interactions at the local level may well impact on other elements within the system. The use of a systems approach in developing the economic model may be helpful in this regard. A systems approach is a broad, conceptual way of thinking about the interactions between parts within a system and with its environment (Squires, 2014). This approach offers a means of exploring and defining the important relevant outcomes within the entire system. It is likely to be overly simplistic to work on the basis that a system can be understood by breaking it down into its individual entities and studying each part separately. By considering the system as a whole, unintended consequences are less likely to be missed.

In situations in which there is more than one relevant outcome, consideration will also need to be given to how these will be presented and/or combined within the HTA process to allow transparent decision making. This is part of the current research agenda (Brazier & Tsuchiya, 2015). Current approaches to generating single index utility outcomes from quality of life synthesise health outcomes from a range of domains. Synthesizing may be appropriate when considering decision making from a single perspective or where all decision makers share the same perspective on outcomes. However it may be a feature of the complex setting that different agents have a different perspective on outcomes, in such cases it may be important to retain a disaggregation of multiple outcomes.

The importance of considering multiple perspectives is likely to be enhanced for complex interventions within a complex setting. Complexity science seeks to understand complex adaptive systems, characterised by large number of agents in open and dynamic environments. By adopting a societal perspective the impact across all potentially relevant agents can be taken into account. However an understanding of how impacts are distributed among different actors is also needed to ensure that the results are relevant to decision making by different stakeholders. The potentially broader range of stakeholders in situations of complexity suggests a more important role for cost consequence analysis (CCA), where comparative costs and consequences of interventions are itemised separately allowing deci-

sion makers to make a judgement about the relative merits of interventions.

The impact of multiple agents will vary between situations where all agents are within the same sector (e.g. health care, social care or public health) decision making and situations where some agents are in different sectors and therefore not all key decision makers are under direct control of the same central policy making. In order to understand the system there is a need to understanding economic incentives of different agents and where these constitute a) barriers / facilitators to intervention effectiveness and/or b) potential areas for intervention.

► **Uncertainty in outcomes**

Additional aspects of uncertainty need to be considered when considering dynamic complex systems. For instance the relation between intervention and outcome may be influenced by unpredictable causal pathways and the influence of context. Interactions within the system are not necessarily linear, due to the impact of positive and negative feedback loops within the system (Lessard and Birch 2010). The interaction of these posi-

tive and negative feedback loops may occur over a long period of time and result in counterintuitive behaviour (Squires, 2014). Again, the adoption of a systems approach offers a means of better understanding these relationships and the uncertainty that they introduce. One practical response to this problem is to incorporate information feedback loops and economic levers within the system to assist in the implementation and management of the intervention and to ensure that the desired outcomes from intervention are achieved. Indeed these outcomes and levers may form an explicit component of the intervention design. Health and wellbeing outcomes may form an important part of such a suite of outcome measures.

9.1.5 Resources and costs

Review of existing guidance

The existing guidances considered identify four key issues in addressing costing within health economic evaluations; the cost perspective, the identification of resources and the measuring and valuation of consumption of these resources.

Outcomes

Recommendations for research

Continuing research into methods for measuring and valuing non-health benefits and appropriate methods for incorporating them into the HTA process is required.

Recommendations for practice

The use of a systems approach to describe the intervention, setting, the agents and interacting components is recommended in order to provide a comprehensive understanding of perspectives and all the relevant outcomes.

The potential relevance of broader health and wellbeing effects need to be explored when considering complex interventions in complex settings.

Where there is a gap between available outcome measures and the needs of decision making, explicit recognition of this gap and its implications should be clearly identified.

At a commissioning level managing the introduction of a complex intervention in a complex system is likely to require consideration of a broad set of outcome measures.

The perspectives for economic evaluation outlined in the national guidance documents have been previously discussed. All guidance, however, makes specific comment on the cost element of perspective. This is particularly important as in each case it defines the scope of resource identification. For example, in Ger-

many the statutory health insurers' perspective implies that all costs to the insurant including non-medical out of pocket expenses are within the scope of economic analysis. The Netherlands, Norway and Italy all specify a societal perspective on costs, although all recognise limitations with implementation. In Eng-

land and Wales the NICE Technology Appraisals guidance is clear in specifying that costs should relate to the resources that are under the control of the NHS and PSS, with broader public service perspectives only being considered in specific cases predefined by the Department of Health. This contrasts somewhat with the NICE public health guidance that recognises the principal need to take a broader public service perspective and further the potential relevance of other stakeholder groups.

The guidance focuses on the scope of resource identification principally driven by the specific perspective of each agency. Thus Germany, The Netherlands and Italy decompose resources into direct and indirect medical and non-medical resources with inclusions and exclusions as appropriate to their respective perspectives. Norway identifies the scope of resources to include the consumption of goods, services, time and physical capital. Where the issue is discussed within the guidance documents there is consensus that medical and non-medical costs occurring in gained life years but not associated with the condition or the treatment should be excluded. The chief impact, identified in the guidance, of selecting a societal perspective is the implied inclusion of productivity impacts. There is methodological debate and lack of consensus around how to include productivity impacts, with Italy recommending the human capital approach and The Netherlands opting for the friction cost method.

Germany and England and Wales provide guidance on the process for identifying resources, with the German guidance suggesting possible published and unpublished literature supplemented by expert opinion and the NICE guidance stating the necessity of demonstrating that use and cost data are collected systematically. There is a common view either explicit or implied that costing requires evidence from a range of sources to be brought together, the German guidance explicitly states that this choice of evidence is a balancing act between relevance, credibility and availability.

With regard to measuring and valuation the German guidance states that whilst identification should seek to generate a complete list of resources consumed, explicit measurement and valuation is not required where the frequency of use or cost is 'judged to have little impact on the results', no guidance on how to make this judgement is however provided. The Norwegian and Italian guidance discusses some methodological problems with identifying appropriate unit

prices of goods and services, relating to the non-existence of equilibrium market prices and the variation in settings and contexts making it difficult to identify generally applicable marginal costs and recommend the use of market prices and charges. Similarly the England and Wales guidance refers to the use of prices relevant to the NHS and PSS. In terms of costing methods guidance from Germany, England and Wales and Italy all make reference to the use of micro and macro costing studies. Within the guidance there is a common concern for ensuring that costs used in assessment are appropriate to the specific country.

Discussion

The primary issues of complexity that affect the assessment of cost and resource impacts are multi-agency, indeterminacy and non-linearity.

The majority of health economics guidance is based upon the assumption that assessment is seeking to support a global decision maker engaged with maximising the efficiency of an overall health system or component programme. The issue of multiple perspectives is recognised in NICE PH guidance on process and methods, however in common with the discussion concerning health and wellbeing outcomes above, the methodological implications for costing are not fully developed. Many PH interventions are complex and guidance and practice in this area raises discussion of many generic issues. Two cases are identified that have qualitatively different potential impacts. Firstly where the costs of a complex intervention and its consequences lie within the domain of local and national government and secondly where they fall outside the government sector and in the wider industrial and social context. Note that these are not mutually exclusive.

NICE PH guidance recognises that PH issues in the UK fall primarily in the scope of local government and that in line with Local Authorities' wider responsibilities for wellbeing, PH initiatives commonly have cost implications outside the traditional health domain, for instance housing, crime and alcohol licensing. Thus costing of interventions and consequences has to take this broader perspective into account. The primary issue being whether and how intersectoral transfers should be identified and implemented. For example a social housing or home insulation initiative may well have important health outcomes (including health equity); therefore should health budgets subsidise, contribute to or financially enable such initiatives and if so how should such costs

be measured? Systematic approaches for identifying the potential direct and indirect cost impacts of pre-defined interventions across a range of stakeholders are therefore required.

Secondly, where the scope of a complex intervention or its consequences lies significantly outside the domain of local or national government then the cost implications of a complex intervention or its consequences might either act as barriers or facilitators to successful implementation or they may give rise to opportunities for economically focused intervention. For example additional costs incurred by an agent may act as a barrier to successful implementation and therefore payments within the system may be necessary to compensate for changes in cost (similar to the public sector intersector transfers above). With respect to economic interventions, consideration of the cost impacts may give rise to interventions aimed at achieving a specified objective, for example subsidies for local fresh fruit and vegetable retailing may be considered as a potential complex public health intervention. Systems approaches that assist in identifying potential financial interventions to achieve defined health and well-being objectives would be beneficial.

Traditional health economic evaluation has benefitted from and to a large extent relies on huge advances in the collection of routine cost and resource data within health systems. Insofar as many complex interventions go beyond the scope of these systems there is a need to cope with variation in quality and availability of costing data. At one level this may simply imply an increased importance for rigorous uncertainly analysis techniques. However, a systemic issue within complex interventions, related to the defining characteristic of indeterminacy, is that the development of definitions and taxonomies is often problematic. This in turn makes the foundation of reliable information systems difficult and gives rise to problems in obtaining adequate data on costs and resources. Examples of this can be found in the palliative care setting and in the screening of new-born children for inborn errors of the metabolism. A similar defining characteristic of complex interventions is the potential of the system to respond to changes in costs within the system. These issues exemplify the need for the development of methods of economic assessment that can cope with rapidly developing health technologies and support economic decision making in evolving environments.

The guidances recognise that there is commonly a high degree of international variation in costs and resources associated both with structural difference between health systems and simple differences in prices. The guidances therefore commonly require economic assessments to either explicitly consider the issue of translation between settings or to undertake country specific analyses. Similarly, a defining characteristic of complex interventions is that they are commonly unrepeatable and are very setting or context specific. The corollary for complex intervention guidance is that there needs to be an explicit consideration of translation between settings or setting specific analyses.

The current guidance on assessment of costs recognises methodological difficulties in obtaining appropriate marginal unit costs for health resources and on more than one occasion recommends using charges as a proxy for costs. Clearly from the perspective of an economic agent in the system, the difference between a marginal unit cost incurred and a tariff charge has the potential to introduce an incentive into the system, which may act perversely for the efficiency of the whole system. For the resources within a co-ordinated publicly funded health system this may not be hugely problematic, firstly because the perception of a coherent goal may exist and secondly the lag between true costs and tariff charges can potentially be managed to minimise the development of perverse practices. The recognition of these issues within health economics focussed on pharmaceutical reimbursement is one of the factors underpinning the investigation of value based pricing and assessment approaches. When considering complex interventions in a disaggregated system the impact of using charges instead of costs may be exacerbated and the impact on assessment may be greater. For example, proposals for pharmaceutical value based pricing focus on obtaining a division of the potential surplus associated with a novel intervention between a supplier and the health system such that the supplier will engage in the market and the health system obtains adequate value for money from the transaction. Where there are multiple potentially competing agents in the system the problem of designing a system that obtains an adequate disbursement of the potential surplus, to ensure that a complex intervention is feasible, delivers value for money and is stable over time (i.e. not subject to evolutionary changes that undermine either feasibility or value) is likely to be even more problematic.

The Norwegian guidance recommends that health economic assessments are subject to discounting of costs (and benefits) at a rate defined by their Ministry of Finance for public projects with moderate systematic risk. This highlights the fundamental relations-

hip between risk, attitudes towards risk and discounting. Where complex interventions in complex systems involve high levels of risk with potentially irreversible impacts stretching far into the future this may have implications for the methods and rates of discounting.

Costs and resources

Recommendations for research

Development of methods of economic evaluation aimed at supporting decision making in the context of rapidly developing definitions/taxonomies relating to resources and costs.

Recommendations for practice

Systems approaches are recommended for identifying resources and costs in complex systems, specifically for:

1. Understanding the location of decision making and the cost perspectives of key agents in the system
2. Obtaining a description of the health system process adequate for the identification of resource items and costs
3. Understanding how interventions may interact with the structure of the process and potential responses and evolution of the process. Identification of consequent changes to resource and cost elements.

Economic evaluations of complex interventions in complex settings should explicitly consider translation of findings between contexts and settings and the limits of their applicability.

9.1.6 Conclusions of the review of existing economic guidance within HTA

The review highlights that intervening in complex systems raises a number of issues for economic evaluation, which are not addressed by current HTA guidance in Europe. The review identifies recommendations for practice. A systems thinking or systems approach potentially provides a useful conceptual framework for addressing some of the issue raised. Specifically use of a systems approach assists in developing an understanding of the decision problem and the scope for economic evaluation, based on an iterative, consultative process and identifying sets of relevant outcomes for decision makers within the system. It can also accommodate an increased role for cost consequence analysis (CCA) to support decision making in the presence of multiple perspectives. Whilst conceptual frameworks exist for structuring the consideration of public health interventions (NICE PH guidance) no similar conceptual frameworks exist for more generic complex interventions. This is the focus of the economic guidance outlined in the following section.

In addition, the review highlights areas where further research is needed, which is beyond the scope of this project. Key characteristics of complexity, including the existence of multiple perspectives and the potential for adaptation and co-evolution are not addressed by current guidelines. Under these conditions assumptions underpinning traditional methods of economic analysis may not hold, for example assumptions regarding stationarity of the system. Furthermore traditional economic approaches aim at maximising a single economic objective function, such as population health (or total quality of life) subject to fixed resource constraints. Considerations of complexity may suggest a move away from such an optimisation paradigm to one of system improvement. Methods for assessing whether the complexity in an intervention/setting matters for economic evaluation are required. Methodological development is required to further understand the potential of computational complexity science methods for changing the role of health economics within HTA in supporting health policy making and the potential of such methods to provide a health economic framework that allows the

role of adaptation, evolution and strategy playing in the health economic market should be investigated. Computational modelling techniques, such as agent based modelling and social network analysis may be useful for understanding the health economic impact of adaptive behaviour and co-evolutions of intervention and setting within HTA. Exploring methodologies to bring evaluation and decision making closer together may be helpful to resolve some of the additional issues raised by complexity within economic evaluations.

Further research into the modelling of behaviour within health economic models is required, along with the development of methods of economic evaluation aimed at supporting decision making in the context of rapidly developing definitions/taxonomies relating to resources and costs. Ongoing research into methods for measuring and valuing non-health benefits in situations of complexity and for incorporating them into the HTA processes will also be important.

9.1.7 References

- ANNEMANS, L., REDEKOP, K., PAYNE, K. (2013) Current methodological issues in the economic assessment of personalized medicine. *Value in Health*, 16, S20-S26.
- ARTHUR, W.B. (2013) Complexity Economics: A different framework for economic thought. SFI Working Paper: 2013-04-012. [Online]. Available from: <http://www.santafe.edu/media/workingpapers/13-04-012.pdf>
- BRAZIER J., CONNELL J., PAPAIOANNOU D., MUKURIA C., MULHERN B., PEASGOOD T, et al. (2014) A systematic review, psychometric analysis and qualitative assessment of generic preference-based measures of health in mental health populations and the estimation of mapping functions from widely used specific measures. *Health Technol Assess*, 18.
- BRAZIER, J., TSUCHIYA, A. (2015) Improving Cross-Sector Comparisons: Going Beyond the Health-Related QALY. *Applied health economics and health policy*, 1-9.
- BIRCH, S., GAFNI, A. (2006) The biggest bang for the buck or bigger bucks for the bang: the fallacy of the cost-effectiveness threshold. *Journal of Health Services Research and Policy*; 11, 46-51.
- CAPRI, S., CECI, A., TERRANOVA, L., MERLO, F., MANTOVANI, L. (2001). Guidelines for economic evaluation in Italy; Recommendations from the Italian group of pharmacoeconomic studies. *Drug Information Journal*; 35, 189-201.
- CARO JJ., NORD E., SIEBERT U., MCGUIRE A., MCGREGOR M., HENRY D., et al. (2010). The efficiency frontier approach to economic evaluation of health-care interventions. *Health Economics*; 19, 1117-27.
- CHILCOTT, J., TAPPENDEN, P., RAWDIN, A., JOHNSON, M., KALTENTHALER, E., PAISLEY, S., PAPAIOANNOU, D., SHIPPAM, A. (2010) Avoiding and identifying errors in health technology assessment models. *Health Technology Assessment*, 14
- COAST, J., SMITH, R., & LORGELLY, P. (2008) Should the capability approach be applied in health economics?. *Health economics*, 17, 667-670.
- COLLEGE VOOR ZORGVERZEKERINGEN. (2006) Guidelines for pharmacoeconomic research, updated version. Valid from April 1st 2006 [online]. Available from: <http://www.zorginstituutnederland.nl/>.
- CRAIG, P., DIEPPE, P., MACINTYRE, S., MICHIE, S., NAZARETH, I., PETTICREW, M. 2008 Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ*, Sep 29; 337: 979-983
- DE SAVIGNY, D., ADAM, T. (eds). (2009) Systems thinking for health systems strengthening. Alliance for Health Policy and Systems Research, WHO.
- DRUMMOND, M.F., SCULPHER, M.J., TORRANCE, G.W., O'BRIEN, B.J., STODDART, G.L. (2005) Methods for the Economic Evaluation of Health Care Programmes.
- GOLD, M.R., SIEGAL, J.E., RUSSELL, L.B., WEINSTEIN, M.C. et al. (eds.) (1996) Cost-effectiveness in health and medicine. Oxford: Oxford University Press.
- INSTITUT FÜR QUALITÄT UND WIRTSCHAFTLICHKEIT IM GESUNDHEITSWESEN (IQWiG). (2009) General Methods for the Assessment of the Relation of Benefits to Costs. Version 1.0-19/11/2009 [Online]. Available from: <https://www.iqwig.de>

- JOHNSTON, M., ZECKHAUSER, R. (2009) The Australian pharmaceutical subsidy gambit: Transmuting deadweight loss and oligopoly rents to consumer surplus, In: Eggleston, K. (ed.) Prescribing cultures and pharmaceutical policy in the Asia-Pacific. Shorenstein Asia-Pacific Research Center, 145-159.
- LESSARD, C. (2007) Complexity and reflexivity: Two important issues for economic evaluation in health care. *Social Science and Medicine*, 64, 1754-1765.
- LESSARD, C., BIRCH, S. (2010) Chapter 13 Complex problems or simple solutions ? Enhancing evidence -based economics to reflect reality. In: Shemilt, I., Mugford, M., Vale, L., Marsh, K., Donaldson, C. (eds.) Evidence-based Decision and Economics: Health care, social welfare, education and criminal justice. Oxford: Wiley-Blackwell.
- LONGWORTH, L., YANG, Y., YOUNG, T., MULHERN, B., HERNÁNDEZ ALAVA, M., MUKURIA, C., et al. (2014) Use of generic and condition-specific measures of health-related quality of life in NICE decision-making: a systematic review, statistical modelling and survey. *Health Technol Assess*, 18.
- LORGELLY, P.K., LORIMER, K., FENWICK, E., BRIGGS, AH. (2014) Outcome measurement in economic evaluations and the role of the capability approach: A review of the literature. [Online]. Available from: http://www.gcph.co.uk/assets/0000/0505/Capabilities_seminar_literature_review.pdf [Accessed : 27.10. 2014]
- MILLER, J.H., PAGE, S.E. (2007) Complex Adaptive Systems: An introduction to computational models of social life. Princeton and Oxford: Princeton University Press.
- NICE (2009) Methods for development of NICE public health guidance (Second edition). National Institute for Health and Clinical Excellence.
- NICE (2013) Guide to the methods of technology appraisal. [Online] Available from: <http://publications.nice.org.uk/pmg9> [Accessed 27.10.2014]
- NORD E. (1999) Towards Cost-Value Analysis in health care? *Health Care Analysis*; 7: 167-175.
- NORWEGIAN MEDICINES AGENCY. (2012) Guidelines on how to conduct pharmacoeconomic analyses. In force from 1st March 2012.
- PAWSON, R. (2006). Evidence based policy: a realist perspective. London: Sage.
- ROBERTS, M., RUSSELL, L., PALTIEL, D., CHAMBERS, M., MCEWAN. P., KRAHN, M. (2012) Conceptual Modeling: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force – 2. *Medical Decision Making*, 32, 678-689.
- ROUND, J., SAMPSON, E.L., JONES, L. (2014) A framework for understanding quality of life in individuals without capacity. *Quality of Life Research*, 23, 477-484.
- SAMUEL, P.S., RILLOTTA, F., BROWN, I. (2012) The development of family quality of life concepts and measures. *Journal of Intellectual Disability Research*, 56, 1-16.
- SCULPHER, M., CLAXTON, K. (2010) Sins of omission and obfuscation: IQWiG's guidelines on economic evaluation methods. *Health Econ*, 19, 1132-6.
- SHIELL, A., HAWES, P., GOLD, L. (2008) Complex interventions or complex systems? Implications for health economic evaluation. *BMJ*, 336, 1281-1283.
- SQUIRES, H. (2014). A methodological framework for developing the structure of Public Health economic models. University of Sheffield.
- SUTTON, E.J., COAST, J.(2014) Development of a supportive care measure for economic evaluation of end-of-life care using qualitative methods. *Palliat Med*, 28, 151-7.
- TAPPENDEN, P., CHILCOTT, J., BRENNAN, A., SQUIRES, H., STEVENSON, M. (2012) Whole disease modelling to inform resource allocation decisions in cancer: A methodological framework. *Value in Health*, 15:1127-1136.
- TASK FORCE FOR THE PREPARATION OF GUIDELINES FOR HEALTH TECHNOLOGY ASSESSMENT. (2009) Guidelines for conducting Health Technology Assessment (HTA) Version 2.1. Agency for Health Technology Assessment, Warsaw, April 2009. [Online]. Available from: www.aotm.gov.pl

- TURNBULL, A.P., SUMMERS, J.A., LEE, S.H., KYZAR, K. (2007) Conceptualization and measurement of family outcomes associated with families of individuals with intellectual disabilities. *Mental Retardation and Developmental Disabilities Research Reviews*; 13, 346-56.
- VALUE IN HEALTH SPECIAL ISSUE. (2009) Moving the QALY Forward: Building a Pragmatic Road, 12, S10 – S15.
- WEISS, C.H. (1995) Nothing as Practical as Good Theory: Exploring Theory-Based Evaluation for Comprehensive Community-Based Initiatives for Children and Families. In: Connell, J. P., Kubisch, A.C., Schorr L.B., Weiss, C.H. (eds.) *New Approaches to Evaluating Community Initiatives. Concepts, Methods and Contexts*. Washington, DC: Aspen Institute.

9.2 APPENDIX OF THE ASSESSMENT OF SOCIO-CULTURAL ASPECTS IN HTA

9.2.1 Literature review on methods to assess socio-cultural aspects of health technologies

Literature search

Extensive literature searches were conducted in 13 databases for publications published between 1970 and 2010. These were updated during the INTEGRATE-HTA project for publications published until September 2013.

Databases searched were MEDLINE, EMBASE, BIOSIS Previews, CINAHL, PsychInfo, Science Citation Index Expanded, Social Sciences Citation Index, Arts & Humanities Citation Index and the Databases of the Cochrane Library (Database of Abstracts of Reviews of Effects, National Health Service Economic Evaluation Database, Health Technology Assessment Database, Cochrane Methods studies, Cochrane Reviews, Cochrane Technology Assessment). Additionally, a hand search in two scientific journals, in Health Policy and in the International Journal of Technology Assessment in Health Care was performed. The search was conducted as from the date of publication of each respective journal until September 2013. Moreover, the reference lists of included publications identified by the literature search in databases were screened.

Due to the variety of socio-cultural aspects, we decided to use a very sensitive search strategy combining MESH-terms and free text terms.³² The keywords were combined and adapted to each database. Specific key terms were:

"(sociocultur* or *sociocultur" or "soziokulturell)"
 "((society or communitt)* and (differen* or disparit*))"
 "societal";
 "mainstream*";
 "perception";
 "social psychology/ or sociology/";
 "sociological aspects";
 "(attitude/ or attitudes*) and (differen* or disparit*)"
 "(attitude to or abortion/ or attitude to aging/ or attitude to aids/ or attitude to breast feeding/ or attitude to change/ or attitude to computers/ or attitude to death/ or attitude to disability/ or attitude to health/

or attitude to illness/ or attitude to life/ or attitude to mental illness/ or attitude to pregnancy/ or attitude to sexuality/ or consumer attitude/ or cultural bias/ or cultural sensitivity/ or exp patient attitude/ or adherence) and (differen* or disparit*)"

"public opinion";

"predjudic*";

(social norm* or cultural norm* or social moral* or cultural moral*);

(cultural belief* or cultural ideas);

"social aspect/";

"(social and (differen* and disparit*))";

"socioeconomics/ or lowest income group/ or poverty/ or socio-economic"

"(inequality* or equity)";

"social status";

"(Health Care System/ or Health Care Utilization/ or health service/ or health care/) and (differen\$ or disparit*)";

"social class";

"social meaning";

"cultural anthropology/ or cultural factor";

"(culture* and (differen* or disparit*))";

"(cultural aspects or cross-cultural aspects)";

"ethnic, racial and religious groups"/ or "ethnic or racial aspects"/ or ethnic difference/ or race difference/ or race/ or ethnic group/ or religious group/ or indigenous people/ or miscellaneous named groups/ or ethnicity. or ethnolog*";

"ethnic identiy";

"health services, indigenous/";

"gender and sex"/ or gender identity/ or gender/ or (gender studies or women's studies or gender gap or gender role)";

"(freedom of choice or patient self-determination)";

"religion"

"conscience"

"(ethic\$.ti,ab. or human rights/ or civil rights/ or exp patient right/ or consumer advocacy/ or fetal rights/ or freedom/ or human dignity/ or patient advocacy/ or personal autonomy/ or reproductive rights/ or right to die/ or right to life/ or social justice/) and (different\$ or disparit*)"

"(freedom of choice or patient self-determination)"

"patient compliance/ or patient participation/ or refusal to participate/ or treatment refusal/ or consumer/ or Health Knowledge, Attitudes, Practice/";

"civilization/ or cultural value/ or social change/";

"(civil or citizen)";

"psychosocial";

"behaviour";

"(applicab* and (differen* or disparities))";

³² The search strategy was developed by Anne Kathrin Stich and Ansgar Gerhardus.

"Biomedical Technology Assessment/";
 "medical technology/";
 "medical technology assessment";
 "health technology assessment";
 "technol* assess*";
 "hta";
 "mta";
 "(evaluation adj technology)".

Selection Criteria

The criteria for inclusion were: 1) Methods for the assessment of socio-cultural aspects are tested or suggested or 2) the publication deals in general with the assessment of socio-cultural aspects of a health technology. We included publications (studies, reviews) that empirically studied social, cultural or socio-cultural aspects of a health technology as well as publications (methodological articles) suggesting a method for the assessment of a health technology. The definition of socio-cultural aspects was kept broad. Publications focusing on ethics or morals combined with socio-cultural aspects were included. 3) The considered publications had to be in English, French, Spanish, German or Dutch.

Publications were excluded if they only considered conceptual frameworks for the assessment of socio-cultural aspects in HTA. A large amount of existing literature on methodological aspects of HTA only mentions methods for considering socio-cultural aspects in few sentences without presenting or explaining them. Publications not particularly focusing on methods were excluded.

Data selection and data extraction

Titles and abstracts of the search results were screened by one author. To ensure a common understanding of inclusion and exclusion criteria samples were screened together before the individual screening process started.

Each included study was appraised by one of the authors. Where difficulties were experienced, the publication was appraised by another author. Aspects to be extracted were the objectives, including the definition or the underlying understanding of socio-cultural aspects, methods for the assessment of socio-cultural aspects, disease, type of technology assessed, country and study population, and time frame.

Results of the literature review

We divided the identified methods into four groups: 1) Checklists 2) literature reviews 3) participatory methods, and 4) methods of empirical social research (publication in preparation).

9.2.2 Overview of INAHTA-agencies that addressed socio-cultural aspects in HTA

We emailed the 56 INAHTA-member-agencies (September 2013) requesting information about their approach to assess socio-cultural aspects of health technologies and also searched through the methods papers presented on the agencies' websites.

We identified ten agencies that addressed socio-cultural aspects in their methods papers or that referred to methods guidance such as the HTA Core Model (EUnetHTA, 2015) or MAST (Telemedicine, 2010) for the assessment of telemedicine applications. The agencies were:

- ▶ the New Zealand National Health Committee (NHC), New Zealand
- ▶ the Canadian Agency for Drugs and Technologies in Health (CADTH), Canada
- ▶ the Australian Safety and Efficacy Register of New Interventional Procedures –Surgical (ASERNIP-S), Australia
- ▶ the Danish Centre for Technology Assessment (DACEHTA), Denmark³³
- ▶ the Healthcare Improvement Scotland (HIS), Scotland
- ▶ the Health Information and Quality Authority (HIQA), Ireland
- ▶ Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA), Austria
- ▶ German Agency for HTA at the German Institute for Medical Documentation and Information (DAHTA @DIMDI), Germany
- ▶ Agency for Health Technology Assessment Poland (AHTAPol), Poland

³³ No longer a member of INAHTA.

9.2.3 Cultural Theory as an example of a theoretical approach to address heterogeneity in HTA

Definition, background and aim

Cultural Theory was first developed to explain differences in individuals' perceptions of risk. Mary Douglas' work on this (e.g., Douglas, 1978) resulted in a theoretical framework allowing for the analysis of different cultural positions. With the idea to combine individual values (incorporation) with ways of social organizations (social regulation), the core of the approach was born. The framework was developed further by political scientists such as Aaron Wildavsky, Michael Thompson, and Michiel Schwarz. A brief summary of the developmental context of Cultural Theory, from looking for the social priorities that base values and priorities, the ambition to overcome a static and deterministic model of analysis, and the necessity of empirical proof linked

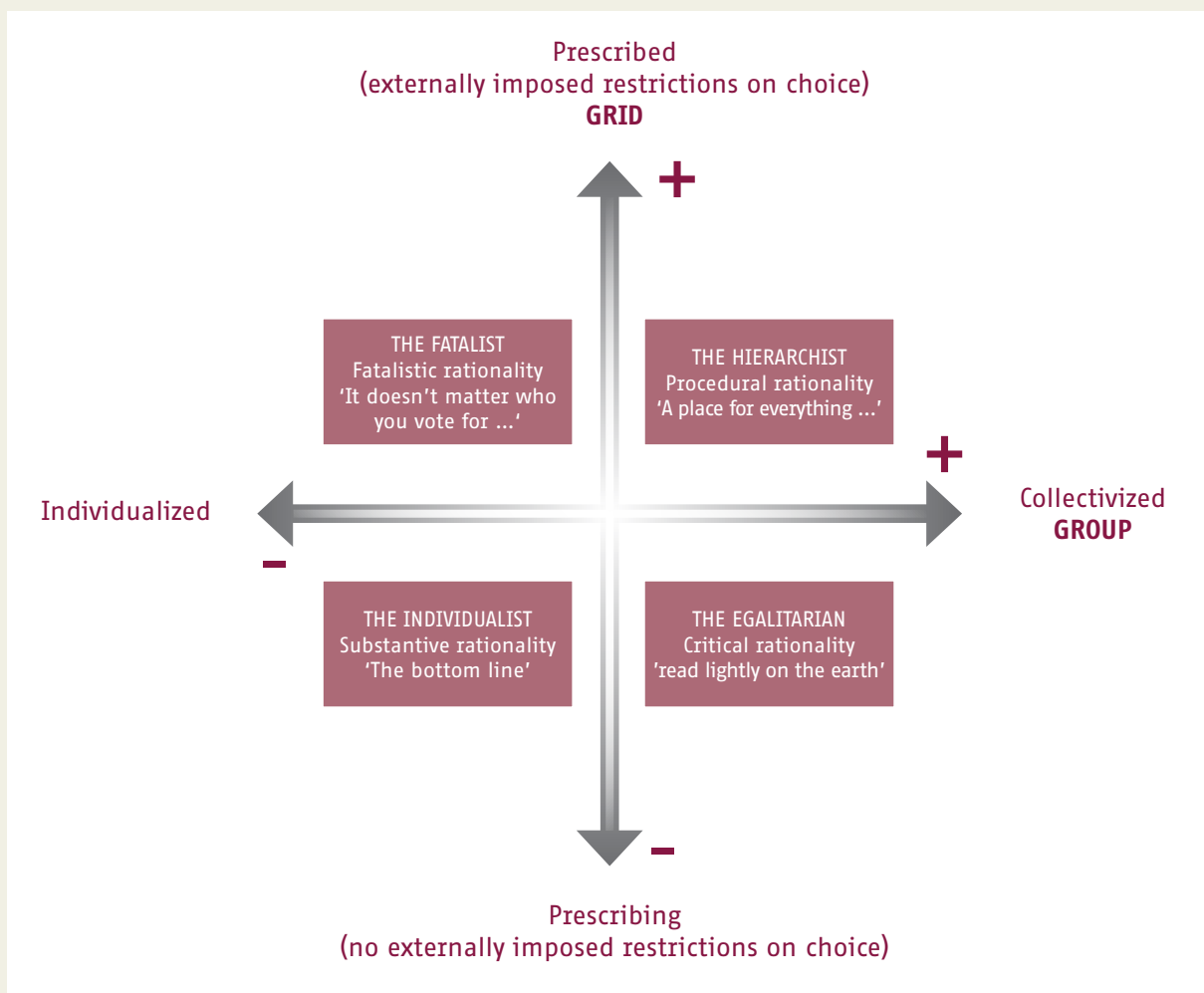
with development and use of research instruments, is given by Douglas (1999, p.412ff.).

The framework was applied in several empirical studies focusing on risk perceptions linked with the implementation of technologies and political decision making (e.g. Dake, 1991; Rayner, 1991), but also in studies on consumption styles and sustainability (e.g. Dake & Thompson, 1999; Douglas, 1992).

The four types of cultural bias

According to Cultural Theory, there are four ideal types representing different cultural rationalities. These are hierarchy, individualism, egalitarianism and fatalism. The cultural types differ in their preferred way of social organization. Each type is characterized by a specific combination of the group and the grid-dimension (see Figure 14). Grid and group always ask for symbolic meaning and social control. The measure of structural constraints a group experiences combined with the measure of group pressure leads to the four

Figure 14: The two dimensions of sociality and the four rationalities.
(Schwarz & Thompson, 1990, p.7)



(respectively five) types of cultures. These four mark the "parsimonious model" (Douglas, 1999) and their mutual competition against each other stabilizes a society's culture. Dynamism results out of the cultures' pursuit to become the dominant one in a certain community (Schwarz & Thompson, 1990).³⁴ The four groups are interdependent and need each other for stabilization.

The four cultural types present four different rationalities. How people act in one cultural context can cause irritation in another. Douglas (1999, p. 411f.) characterizes the four types as follows: "Of four cultural biases, the first (...) supports tradition and order; its hierarchical form of organization is good for solving problems of coordination. (...) individualism; it holds no brief for tradition for its own sake; its form of organisation is competitive, with dominant positions open to merit. These two correspond for all intents and purposes to the Weberian distinction between bureaucracies and markets that has worn so well in the social sciences. (...) Most social theory is based upon minor variations of these two contrasted cultures, but Cultural Theory allows for a third quite different type (...) which corresponds to the closed egalitarian system. Organisationally it is the closed sectarian community that has elaborate rules for keeping themselves equal. Instead of exalting leaders (...) in this type of culture ambiguous leaders are dragged down, and often expelled. The fourth cultural type (...) [fatalism, KM] is the option for anyone who avoids alignment, and who for whatever reason does not expect or intend to lead or to follow, to persuade or to organise".

Hierarchical culture:

"When an individual's social environment is characterized by strong group boundaries and binding prescriptions, the resulting social relations are hierarchical. Individuals in this social context are subject to both the control of other members in the group and the demands of socially imposed roles. (...) The exercise of authority (and inequality more generally) is justified on the grounds that different roles for different people enable people to live together more harmoniously than alternative arrangements" (Douglas 1982 quoted by Thompson et al., 1990, p. 6).

"The upper-right quadrant of the cultural scheme

(positive group/ positive grid (...)) is the natural environment of highly prescribed institutional action, where group loyalty is rewarded and formal status distinction respected. It belongs to the hierarchy, where every member knows his or her place, securely bounded and un-ambiguously stratified. Keeping things in their places, transactions in their proper channels, and parts subservient to the whole are the actions that must be fostered if stability is to be achieved. This political culture, therefore, can be characterized as biased towards ritualism and sacrifice" (Schwarz & Thompson, 1990, p. 75).

Individualist culture:

"Market cultures stress the autonomy of individuals and their resulting freedom to bid and bargain with each other: they have substantive rationality. The bottom line is what they care for, not the relational niceties of the people who happen to have come together to achieve that result" (Schwarz & Thompson, 1990, p. 6).

"In the diametrically opposite corner of the social context space [hierarchy, KM] (negative group/negative grid) individuals have ample freedom for negotiating relationships on the basis of contractual exchanges. This social environment allows for maximum individual mobility up and down whatever the scale of authority or influence. Here one finds the ideal-type free market organization, characterized by the proliferation of ego-focused networks and by entrepreneurial activity aimed at private profit seeking of all kinds. The individualist expands his network in all promising directions; he has no interest in the maintenance of permanent transactional boundaries. The market institution is stabilized by the view that anything is negotiable in the pursuit of personal rewards in a competitive environment. The individualistic political culture is biased towards pragmatic materialism." (Schwarz & Thompson, 1990, p. 75).

Egalitarian culture:

"Egalitarians believe that human beings are born good but are corrupted by evil institutions. (...) This optimistic view of human nature is essential to the viability of egalitarian social relations (low levels of prescription within a communitarian setting). By making man (and woman) naturally good, egalitarians can persuade

34 "That no way of life can exist alone does not mean that every way of life will be equally represented within a single country at a given point in time. (...) The differences between regimes, therefore, are to be found in the differing configurations of this perpetual dynamic imbalance between the five ways of life" (Thompson 1990, 4).

de each other that 1) uncooperative behaviour is a product of the false consciousness that coercive institutions have imposed on individuals (thereby justifying the efforts of egalitarians to raise the consciousness of other) and that 2) a no coercive (low-grid) and cooperative (high-group) social environment is a viable way of organizing life" (Thompson et al., 1990, p. 34).

"Since the third institutional type is organized as a bounded egalitarian group (sometimes called a clan, or a club or a sect or an equity), it scores high on the group dimension. Its members are collectively protective against the outside world. It is bound together by a common set of ideals to which all members voluntarily subscribe (...). It rejects, however, the hierarchy and all the prescriptions and institutionalized inequalities that characterize highly stratified contexts. That is, it scores negatively on the grid dimension. Authority resides not in the individual, nor on the basis of status, but in the collectivity as a whole. The bias of this egalitarian political culture is towards fundamentalism (just one vital boundary to protect) and millenarianism (the perfect world we will all enter when that boundary no longer has to be protected)" (Schwarz & Thompson, 1990, p. 75).

Fatalistic culture:

"Isolates, by choice or compulsion, literally alone or isolated in complex structures", "... anyone who avoids alignment, and who for whatever reason does not expect or intent to lead or to follow, to persuade or to organise", "...the more that the persons in this position are alone, the less can they predict or interpret what is going on, hence they tend to a culture of fatalism" (Douglas, 1999, p. 412).

"In moving from individual behaviour to the level of institutional behaviour pertinent to public policy making, Cultural Theory suggests that one of the four cultural strategies will not be actively present in the policy arena. Given the continual pressures upon the fatalist by those sub-scribing to hierarchical authority, by successful individualistic competitors, and by boundary-maintaining egalitarians, this social type is excluded at the level of institutional interaction. Fatalists find it impossible to involve themselves with lasting, socially viable group or network relations, and are incapable of participating in public policy debates. They have enough on their short-term plates just

coping with the vagaries of their unpredictable and uncontrollable environment ('why bother the vote', they will rationalize, 'the government always gets in'). The individual caught up in this positive grid/negative group social context has scope for neither autonomous personal transactions nor group immersion. His behaviour is entirely restricted by the social prescriptions that others have thrust upon him. (...) It is for that reason that the fatalists are crucial to policy debates, even though they play no active part in them. Fatalists have to rely on the other institutional types to speak on their behalf (which they do, each in its distinctive way). Alternatively, of course, they can try to migrate to other social contexts the fatalist's political culture is biased towards an inconsistent eclectism. It is, to those looking down on it from the outside, a kitsch assemblage presided over by Lady Luck" (Schwarz & Thompson, 1990, p. 76).

A detailed overview of the different attributes characterizing the four specific types (e.g., risk perception, social control, preferred economic model etc.) can be found in (Schwarz & Thompson, 1990, pp. 66-67).

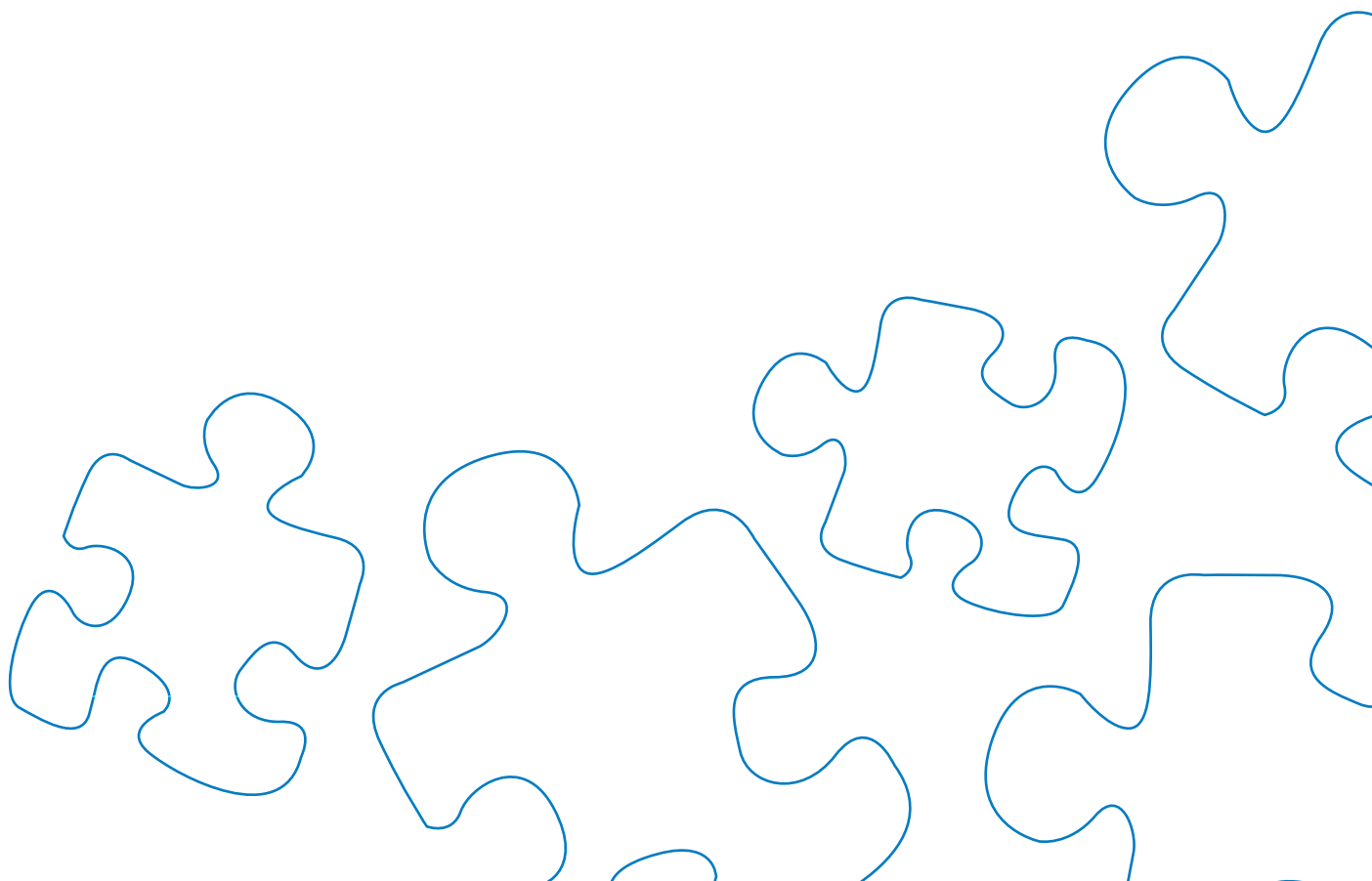
Using Cultural Theory in the socio-cultural assessment of health technologies

Based on the idea of Constructive Technology Assessment, technology is understood as interwoven in social processes. Social assumptions underlie the idea of the technology itself as well as of its viability and the way it is organized. Understanding background ideas of perspectives ensures a reflexive learning process, which could be offered by HTA. "These may involve: Implicit judgements of the institutions that supposedly control the risky activities, which judgement also affects the defined scope and nature of the risk problem; models of social relations and processes involved in operating, maintaining and regulating the technology, which models include assumptions of deterministic rule-following that conceal indeterminacy in such systems; and experts' implicit constructs of the public as risk definer and political actor" (Wynne, 1995, p. 30).³⁵ Cultural Theory offers a way to identify different perspectives on a certain technology. Differences can be mutually linked with each other to generate a better understanding of success or failure of a technology in a specific cultural context and the level of social policing that is required. Questions such as "What

³⁵ "These kinds of framing social assumptions carry strong but unstated value commitments. They take on the role of prescription precisely because conventional discourses of risk and technology lack recognition of the essentially open, socially constituted character of technologies, and the mutual construction between technology and social context of validation. They cannot be recognized and articulated in public debate without a more reflexive approach which transcends the language of impacts, even if this language takes us inside the black boxes" (Wynne, 1995).

would it be like to use a health technology in one of the different cultures?", "Will there be different attitudes about implementing health technology?" and "How would different professional cultures influence the health service/ providing the health technology?" can be answered using Cultural Theory. The focus is on social individuals (not just individuals that have preferences, but who are involved in social relationships and structures of power).

The presented socio-cultural framework developed in the INTEGRATE-HTA project presents several aspects (framework categories, respectively) linked with a health technology. To show how Cultural Theory can be used to capture heterogeneity of all of these aspects, we applied it to all framework categories. Cultural Theory can be used on different aggregation levels e.g., on the micro-level, when treatment decisions between patient and physician are made or on the macro-level where (cultural different) decision makers decide about a technology's implementation). Furthermore, through weighing the cultural differences higher than nationalities the theory offers an option for the analysis in different national contexts.



9.2.4 Framework categories reflected against the background of Cultural Theory

Social construction of health issue

Table 27: Framework main category: Social construction/understanding of health issue.

Aspect of interest for socio-cultural assessment:	Social construction of health issue/ understanding of health issues the technology addresses
"Social construction of health issue" from the perspective of cultural biases	
Benefit of using Cultural Theory	Cultural Theory facilitates the identification of cultural differences in constructing health issues (e.g., how are they defined, which treatment is seen as the "right" one etc.). Each cultural type refers to a different idea of (physical) nature, which underlies the specific understanding of health and related phenomena.
hierarchical	In the hierarchical context definition and treatment of health issues are highly professionalized and institutionalized. Health knowledge is structured and organized following generally accepted guidelines (e.g. ICD, ICF). Following the idea of nature seen as perverse/ tolerant health issues are rather defined in a dualistic way (normality vs. abnormality) than in a continuous way. It emphasizes specific parts rather than a holistic view of health. Medical experts (defined by explicit role descriptions) are responsible for diagnosis and treatment (based on "objective knowledge"/ institutionalized authority). They also decide about the patient's ability to fulfil other social roles (e.g., as employee). Patient's subjective perception and understanding of health issues are less relevant.
individual	<p>The individualist's perspective on health issues is more pragmatic. Apart from nearly complete knowledge (hierarchy) patients decide about importance of a health issue and necessity of treatment as well as about treatment options (e.g. paying for them by themselves).</p> <p>Individual freedom is emphasized in this context. Due to potential limitations of individual freedom professional authority is questioned. Expert decisions are just one option of dealing with health issues next to a variety of others accessible on the market. Individualism is linked to economic interests of providers. Patients' subjective perceptions and understanding of health issue are taken seriously – at least because they are seen as consumers. Consequently, specific technical facilities of different practices or hospitals could lead to an increasing number of specific diagnoses that need to be treated using these facilities. Besides risk orientation and medicalization can increase through selling the idea of certainty (e.g. non-evidence based interventions to identify several risks during pregnancy).</p>
egalitarian	The egalitarian view characterizes a deep scepticism against institutions and how they define and deal with health issues. Egalitarians criticize hierarchists' and individualists' ways of addressing health issues, e.g. due to medicalization, disease mongering or over- and under treatment. The empowered patients' subjective views and experiences are central for egalitarians. The more holistic concept of the body as a natural phenomenon is linked with an understanding of health as a continuum. Egalitarians strongly criticize misuse of resources and non-holistic perspectives as they characterize the concept of nature ephemeral. This can be transferred to the human body.
fatalistic	Fatalists are characterized as "isolated in complex structures" (Douglas, 1999, p. 412). That means: If their health complaints are taken seriously it is okay, if not it is bad luck. Fatalists randomly follow one of the other cultural ways. Knowledge about health issues is irrelevant (everything is equal). Against the background of the fatalist's concept of "nature capricious", health and illness are seen as unpredictable. There is no possibility of control.

Table 28: Framework subcategory: *Perceived usefulness and the idea of benefit.*

Aspect of interest for socio-cultural assessment:	Perceived usefulness and the idea of benefit
Subcode of:	Social image of technology and use
Benefit of using Cultural Theory	The socio-cultural context influences the definition and evaluation of the benefit of health technologies. The variety of priorities and preferences could lead to heterogeneous (conflicting) assessment results that need to be taken into account politically. Furthermore, the cultural imprint of assessment procedures itself becomes transparent and aware.
“Perceived usefulness and the idea of benefit” from the perspective of cultural biases	
hierarchical	Extensive classification and programming is used to solve coordination problems. In the hierarchical context (Douglas 1975, 4). The protection of society is based on controlling information and “channeling wealth to established authority” (Thompson et al. 1990, 180). Benefit is defined institutionally (traditional) by the authoritative government. Experts are the ones with justified power in evaluating the safety zone (Mamadouh, 1999, p. 402). This power is legitimized in specialized competency (institutional perfectionism) or in their specific morality and integrity (communitarianism) (Hendriks 1999, 429). The benefit assessment is characterized by bureaucratization. It is based on the anticipation of balanced short and long-term consequences of technology use.
individual	The individualist idea of benefit and perceived usefulness is based on individual rationality (Thompson et al., 1990, p. 97). This cultural type of acting seeks to reduce authority. Benefit definition and political decision making are based on the (indirect) control of the market, which is the general mechanism of conflict resolution. Decision makers change because of non-permanent social rankings of cultural groups. Boundaries are provisional and subject to negotiation. Individualists are open to try new things out – especially if they seem to be attractive for the market. Changing individual needs decide about the idea of benefit as well as economic advantages. Benefit assessment is based on trial and error. Short term consequences linked with the technology dominate the long term. The knowledge they refer to is pragmatic instead of nearly complete and consistent (hierarchy).
egalitarian	Deep skepticism against institutions and authority characterize egalitarian evaluations and decision making in general. Both the hierarchical and the individual culture are to be blamed. They make institutions and over-technologization responsible for alienation from human nature. Critical discussion (using an established interest group system) and participatory decision making constitute the way of defining benefit and characterize the benefit assessment. Aiming for sustainability egalitarians take moral issues into account and focus on collectivity. Equity and social inequalities caused by the technology are considered (see also “social inequality and technology use”).
fatalistic	Fatalists believe in fate. They don’t have access to political decision making and no preferences. Dependent on the decisions made by the other three cultural biases fatalists try to cope passively as best as possible focusing on the present and not on the future.

Social image of technology and use

Considering different cultures in the analysis of the social image of a technology reflects on how the technology is seen and accepted in different cultural

contexts. This can explain why technologies work in a certain context (that context it is developed for) but fail in another. Differences in evaluation and decision making become transparent and can improve the democratization of the HTA-process.

Table 29: Framework subcategory: Knowledge about and understanding of technology.

Aspect of interest for socio-cultural assessment:	Knowledge of technology
Subcode of:	Social image of technology and use
Benefit of using Cultural Theory	The socio-cultural context influences the definition and evaluation of the benefit of health technologies. The variety of priorities and preferences could lead to heterogeneous (conflicting) assessment results that need to be taken into account politically. Furthermore, the cultural imprint of assessment procedures itself becomes transparent and aware.
"Knowledge about and understanding of technology" from the perspective of cultural biases	
Benefit of using Cultural Theory	Cultural Theory identifies and reflects on different kinds of knowledge. It becomes visible how perceived usefulness and the idea of benefit is shaped by the knowledge the four cultures refer to when assessing the technology. Besides, the analysis can help understand why a certain knowledge/rationality is set over others in the decision making process. Issues of negotiation and mutual misunderstandings that are part of decision making become more transparent.
hierarchical	Hierarchists rely on knowledge that is objectivized by institutionalized expert' authority. They don't trust individual rationality but tradition (Thompson et al., 1990, 97). "Both assume that authoritative government requires special qualifications, either in terms of merit and competency (institutional perfectionism) or in terms of morality and integrity (communitarianism)" (Hendriks 1999, 429). It is clearly regulated which questions are answered by which profession and status distinctions are respected. "Almost complete and organized" is the scope of knowledge that is typically for hierarchists (Schwarz & Thompson, 1990, p. 66).
individual	Individualists trust in the regulation of the market and individual rationality. The knowledge type they refer to is substantive, sufficient and timely (Schwarz & Thompson, 1990: 66). Knowledge about the technology is gathered by trial and error. They focus on short term consequences (ibid).
egalitarian	Typical for the egalitarian way of shaping the image of a technology is their critical rationality. The idea is to falsify theory to detect truth. Knowledge is imperfect but holistic (ibid). No authorities (neither institutions nor the market) are able to decide about right knowledge.
fatalistic	Fatalists' nature is unpredictable. They believe in fate. Knowledge is irrelevant because they are not involved in active decision making ("what you don't know, can't harm you" (Thompson et al., 1990, p. 63).

Table 30: Framework subcategory: Attitudes and acceptance of technology and use.

Aspect of interest for socio-cultural assessment:	Attitudes and acceptance of technology and use
Subcode of:	Social image of technology and use
"Attitudes and acceptance of technology and use" from the perspective of cultural biases	
Benefit of using Cultural Theory	Cultural Theory can help identifying culturally different attitudes of users and decision makers in a structured way. This could facilitate exchange about critical issues, preferences, advantages and disadvantages. Through integration of different perspectives, HTA becomes a democratic social learning process.
hierarchical	Attitudes against and acceptance of technology and use in the hierarchical context are influenced by institutional authority and tradition. Strong group opinion represents the institutional context (linked with authority). Structured knowledge and anticipation of risks given by experts (strong external role prescriptions) shape attitudes and acceptance.
individual	Individualists' attitudes against technology are characterized by economic rationality, i.e. pragmatic materialism and substantive rationality. Not authority but self-regulation and the mechanisms of the market influence the shape. The social context is distinguished by low group relations and low social control. Individualists are fashion conscious (not traditionalists) what could also influence their perspective on new technologies.
egalitarian	The egalitarian culture emphasizes critical reflection and mistrusting institutions as well as technologies. Acceptance of a technology is just possible if no undesired consequences are identifiable. Social inequalities in access or as a consequence of the implementation of a technology have to be identified, discussed and questioned. Collectivity is the central focus of assessment due to high values in group and grid.
fatalistic	Based on their marginalized social position attitudes of fatalists are not relevant in the process of decision making. They cope with the decisions made by the other three groups. Fatalists randomly try to cope with what is given to them. They don't trust in technology just as they don't trust other people. Acceptance of technology in that context is a result of being led by others as well as of luck and fate.

Table 31: Framework subcategory: Risk perception and handling.

Aspect of interest for socio-cultural assessment:	Risk perception and handling
Subcode of:	Social image of technology and use
Benefit of using Cultural Theory	The socio-cultural context influences the definition and evaluation of the benefit of health technologies. The variety of priorities and preferences could lead to heterogeneous (conflicting) assessment results that need to be taken into account politically. Furthermore, the cultural imprint of assessment procedures itself becomes transparent and aware.
"Risk perception and handling" from the perspective of cultural biases	
Benefit of using Cultural Theory	<p>Cultural Theory offers a frame to describe culturally different ways of perceiving/seeing and handling risk from the perspective of users, providers and decision makers. "The perception of risk is a social process. Preferences for risk, we argue, can be explained by the function those preferences serve for an individual's way of life" (Thompson 1990, 63).</p> <p>Based in the way cultural types see nature and resources the definition, assessment and measurement of risk varies. Knowledge about the four perspectives leads to a reflective assessment characterized by exchanging different views. Besides it would become transparent that political decision makers refer to different ways of risk perception and handling influenced by their cultural context.</p>
hierarchical	<p>The hierarchical way of seeing and handling risks is characterized by justified expert' knowledge and authority. It is authoritative and explicitly controlled. In the case of failure responsibility is shifted away from the institution: "Hierarchists are famous for their blame shedding techniques. Responsibility is hidden or (...) diffused among numerous officers.</p> <p>Investigators are quashed or forbidden by Official Secret Acts. Blame is shifted to deviants, who do not know their place and must be subject to reeducation or sent to asylums" (Thompson 1990, 59). The most important risk for that kind of culture is to lose control (i.e. of public trust) (Thompson et al., 1990, p. 66f.).</p>
individual	Individualists have a different way of risk taking. Instead of trusting external authority they are open minded for pragmatic experimentation, believing in a nature that is friendly and resourceful and in the ideal of self-regulation (Wildawsky, 1987, 6). They believe in healthy competition between willful people and dislike being subjects of group decisions (Hendriks 1999, 428). Risk is taken as opportunity (Thompson 1990, 63). Threats to the functioning of the market (e.g. through institutionalized/ political control) are the biggest risk for that kind of culture (ibid).
egalitarian	The critical rationality of egalitarians mistrusts the institutionalized way of risk assessment and handling as well as individual's pragmatic risk taking. For egalitarians (human) nature is fragile and needs to be protected for any potential harm. Technology as well as institutional rationality is related to risks of alienation from nature. "Any system that would impose hidden, involuntary, and irreversible dangers on people is not to be trusted (it is safer in the egalitarian group)" (Thompson 1990: 63).
fatalistic	Fatalists perceive nature as unpredictable and distrust others. Having no possibility of control leads to the "apathetic culture" (Wildawsky 1987, 7) trying to cope as good as possible with the things that happen to them. The identified style of risk handling is "acceptance and absorption" (Thompson et al., 1990, p. 67).

Social aspects of implementation of technology/ organization of technology use

Table 32: Framework subcategory: Socio-cultural characteristic of target group.

Aspect of interest for socio-cultural assessment:	Socio-cultural aspects of target group
Subcode of:	Social image of technology and use
Benefit of using Cultural Theory	Cultural Theory offers a structured way to understand how different cultural groups view/ experience the organizational structures and implementation modes. The cultural context of individuals in treatment situations as well as the cultural context of decision makers is the basis for treatment or political decisions. Various information on how the technology is socio-culturally embedded could identify tensions, e.g. between the process of development, implementation, assessment and decision making (links to "social image of technology and its use").
"Socio-cultural aspects of target group" from the perspective of cultural biases	
Benefit of using Cultural Theory	The analysis of cultural context makes differences such as the idea of being a patient between and in target groups transparent.
hierarchical	The hierarchical context is characterized by prescribed (traditional) role definitions. The role of professionals is as clearly defined as the role of patients. Patients are seeking for expert advice and knowledge. Desired treatment outcomes and necessities will mostly be defined by physicians than by patients. Asking patients for their preferences could cause confusion in that cultural context.
individual	Active decision making of patients is valued higher than expert' advice in the individualist context. Being an informed patient means knowing about available options on the market and asking for them. If one treatment does not succeed, individualists will exit e.g. the institutional context and search for other opportunities. Entering different institutions/ treatment contexts for individual benefit can lead to the use of (contradictory) options in parallel. New technologies are seen as chance. Trial and error will decide about the "right" treatment.
egalitarian	Being an informed patient also characterizes the egalitarian context. However, patients ask for information to enable themselves to make self-determined decisions (not because of knowing the market). Egalitarians want to be informed because they don't trust the other treatment cultures. Fears of alienation from natural human's habitats and the overall objective of protecting the collective need to be addressed looking at target groups in that cultural context. Priorities are critical weighing, independent information (on technology and health issue), distrust in authority and empowerment.
fatalistic	Fatalists have no treatment priorities. Due to their passivity they will often refer to the hierarchical context with differences in treatment outcomes (e.g. they don't follow expert's advice because they don't believe it will change anything). Due to their low grid and group levels the importance of significant others in treatment decisions will be lower. Luck will decide if the „right“ direction was coincidentally chosen.

Table 33: Framework subcategory: Social inequality and technology use.

Aspect of interest for socio-cultural assessment:	Social inequality and technology use (incl. stigmatization and discrimination)
Subcode of:	Social aspects of implementation of technology/ organization of technology use
"Social inequalities and technology use" from the perspective of cultural biases	
Benefit of using Cultural Theory	Cultural Theory facilitates the identification of different perspectives in a structured and transparent way. A clearer picture of the cultural conditions of social inequality will help to understand how different groups handle and value it.
hierarchical	"Equality before the law" (Schwarz & Thompson, 1990, p. 66) is distinguishing the hierarchists' perspective on inequality from the others. However, due to the hierarchical structure social inequalities are inherent in the system and are a basis for its stability that is traditionally rooted in prescribed roles, authorities, and the acceptance of status distinctions (high group/ high grid). Social inequalities are legitimized with the wealth and interests of the public framed by institutions.
individual	Social inequalities are also part of the individualists' cultural context. They are legitimized in individual freedom. Due to low boundaries rooted in traditional roles or status distinction the individual is relatively free when making decisions. As a consequence social inequalities are not stable. Change is a result of individual acting, taking part in fair competition. Access to information and treatment is decided on the market following economic rules and the belief in "equality of opportunity" (Schwarz & Thompson, 1990, p. 66).
egalitarian	Egalitarians' critical rationality is based on mistrusting institutions and the market system. The cultural bias is deeply characterized by the ideal of equality and the reflection of (hidden) inequalities. Egalitarians set it upon themselves to protect equality between different people and groups. Awareness of differences and their legitimization is given: „The crucial question is not whether there are large differences in individual or group resources – surely there are – but whether these are viewed as natural or unnatural, right or wrong, appropriate or illegitimate" (Thompson 1990: 60).
fatalistic	There is no general idea about social inequality. Fatalists believe in and blame fate.

Table 34: Framework subcategory: User-professional-relationships and decision making.

Aspect of interest for socio-cultural assessment:	User-professional relationship and decision making
Subcode of:	Social aspects of implementation of technology/ organization of technology use
"User professional relationship and decision making" from the perspective of cultural biases	
Benefit of using Cultural Theory	The cultural context shapes the relationship between users and providers (and as a consequence the process of decision making) differently. Consequently, the understanding of the relationship and whether people fit in the offered frame influence the success of treatment. The description of cultural mechanisms shows whether and how a technology fits in a certain cultural context and whether and how the transfer to another context is possible. Cultural Theory helps identify user preferences as well as different ways of shaping relationships with professionals. Cultures of institutionalized contexts (e.g. hospital compared to private practice) become visible.
hierarchical	Authority, expert knowledge and prescribed social roles (e.g. patient's and physician's role) are part of the hierarchical context. The relationship is shaped in a traditional way with authority on the expert's side and a tendency of passivity on the patient's side. Autonomy is limited. Informed patients questioning institutionalized authority can be seen as difficult. Additionally (medically) specialized knowledge is given priority over a holistic approach.
individual	Individualists enter institutional contexts only if they foresee personal advantage. Autonomy (understood as „choice of options“) and individual freedom to use the opportunities on the (treatment) market characterize how preferences are established and revealed. The patient's and provider's role become more adjusted to the mechanisms of the market and commercialism. This can be linked to technologies that are offered (sold) to the patient (consumer).
egalitarian	Participatory decision making characterizes the egalitarian preference for treatment decisions. Autonomy and information needs to be evaluated critically also in terms of social inequalities that could be linked with a treatment decision. Skepticism against institutionalized and hierarchical structures could lead to fears of losing autonomy (e.g. in a hospital) and be linked with mistrusting treatment decisions made in that cultural context.
fatalistic	Fatalists don't have treatment preferences. Characterized by passivity and not wishing to know more about complex issues („not knowing means no harm“ (Thompson 1990, 63), fatalists will behave „inconsistently eclectic“ in treatment contexts (Schwarz & Thompson, 1990, p. 66).

Table 35: Framework subcategory: Relationships between professionals providing the technology.

Aspect of interest for socio-cultural assessment:	Relationships between professionals using the technology
Subcode of:	Social aspects of implementation of technology/ organization of technology use
"Relationships between professionals using the technology" from the perspective of cultural biases	
Benefit of using Cultural Theory	Cultural Theory enables the reflection on different modes of cooperation and the understanding of whether ways of cooperation fit in a specific cultural context. Mismatches could be a reason of technologies' failure.
hierarchical	Professional cooperation in this context is characterized by hierarchy. Decision making and responsibility are linked with professional and social status. In hierarchic teams, decision making about treatment options is based on medical knowledge and (specialized) physicians' opinions.
individual	Cooperation between professionals in this context can be seen as being of economic interest (e.g. sharing specific (and expensive) equipment, transferring patients to colleagues for further treatment options). Authority is not part of that organizational culture (and if then it is not as stable as in the hierarchical process).
egalitarian	Egalitarians avoid authority and criticize institutionalized structures as well as market oriented practices. (Interdisciplinary) team members are equal by status (no matter what profession). Hierarchy is obsolete. Knowledge is shared and team colleagues learn from each other. Decision making takes part from bottom up and is shaped as participatory process. Responsibility is shared. Teams work together for a common value (could be a specific understanding of the intervention/ technology).
fatalistic	/

9.2.5 References

- DAKE, K. (1991) Orienting dispositions in the perception of risk: an analysis of contemporary world views and cultural biases. *Journal of Cross-Cultural Psychology*, 22, 61-88.
- DAKE, K., THOMPSON, M. (1999) The Meaning of sustainable development: household strategies for managing needs and resources. In: WRIGHT, S. D. E. A. (ed.) *Human Ecology: Crossing Boundaries*. Fort Collins, CO: The Society for Human Ecology.
- DOUGLAS, M. (1978) *Cultural bias*, London, Royal Anthropological Institute of Great Britain and Ireland.
- DOUGLAS, M. (1992) In defence of shopping. In: EISENDLE, R. M., E. (ed.) *Produktkulturen und Bedeutungswandel des Konsums*. Frankfurt: Campus.
- DOUGLAS, M. (1999) Four cultures: the evolution of parsimonious model. *GeoJournal*, 47, 411-415.
- EUnetHTA JOINT ACTION 2, Work Package 8. HTA Core Model @ version 2.1 (2015). Available from: <http://www.corehta.info/BrowseModel.aspx>.
- HENDRIKS, F. (1999) The post-industrialising city: political perspectives and cultural biases. *GeoJournal*, 47, 425-432.
- MAMADOUH, V. (1999) A political-cultural map of Europe. Family structures and the origins of differences between national political cultures in the European Union. *GeoJournal*, 47, 477-486.
- RAYNER, S. (1991) A Cultural Perspective on the structure and implementation of global environmental agreements. *Evaluation Review*, 15, 75-102.
- SCHWARZ, M., THOMPSON, M. (1990) *Divided we stand. Redefining politics, technology and social choice*. Philadelphia, University of Pennsylvania Press.
- TELEMEDICINE, M. N. C. F. I. C. A. (2010) *MethoTelemed. Methodology to assess telemedicine applications*.
- THOMPSON, M., ELLIS, R., WILDAVSKY, A. (1990) *Cultural Theory*, Boulder, CO, Westview Press.
- WYNNE, B. (1995) Technology assessment and reflexive social learning: observations from the risk field. In: RIP, A. M., THOMAS; SCHOT, JOHAN (ed.) *Managing technology in society. The approach of Constructive Technology Assessment*. London and New York: Pinter Publishers.

9.3 APPENDIX OF THE ASSESSMENT OF LEGAL ASPECTS IN HTA: COMMON LEGAL PROVISIONS WITHIN THE EU

Although there is no such thing as a consistent EU health law (Tamarak & McHale, 2004, p. 4), many EU regulations concern legal areas affecting health care: Besides the obligation to “health mainstreaming” (i.e. the consideration of health issues and the promotion of public health in all Union action) in Articles 9 and 168 TFEU (Treaty on the Functioning of the European Union) legal action of the EU can be legally well-founded by different provisions of the TFEU such as those on free movement of goods, services and workers, competition law and so on. (Barnard & Peers, 2014, p. 622). Moreover, health law is affected by the provisions of the Charter of Fundamental Rights (CFR) and the European Convention on Human Rights (ECHR). Although the latter one is not a Convention of the European Union but of the Council of Europe, it is binding for the Member States of the Council and regarded as sources for the interpretation of community law by the ECJ.³⁷ Also of importance for the practical HTA-work, often even of bigger importance than the above said sources, is the so called EU-secondary law, especially directives and regulations. While the latter are (with few exceptions) “self-executing”, i.e. no implementation in national law is necessary, directives are only binding as to the result to be achieved and therefore oblige the Member States to enact a national transpositional act according to the directive's provisions (Chalmers, Davies & Monti, 2014, p. 112). This means that a search for the national implementation is required for every relevant directive identified. The applying national laws can mostly be found by searching for the directive in national legal databases.

9.3.1 Provisions concerning the patient

Privacy

Most European provisions concerning the patient can be summarized under the term “privacy” which is an umbrella term for a number of rights of the individual. The term is strongly influenced by an article of Warren and Brandeis in 1890 (Warren & Brandeis, 1890) in

which the right to privacy is defined as “the right to be let alone”. This right contains the negative component of defending the private sphere against unauthorised interference as well as a positive component, allowing the individual to decide autonomously in all private matters (Buchner, 2015). European norms addressing the right to privacy can be found in Art. 7 CFR as well as Art. 8 ECHR, both stating that everyone has the right to respect for his private and family life, his home and communication.³⁸ The right to privacy encompasses many rights, for example but not only right to physical and mental freedom (also protected under Art. 6 CFR) the right to physical and psychological integrity (also protected under Art. 3 CFR) which is one root for the autonomy of the patient and the resulting autonomous and informed consent of the patient: Examinations, taking of body samples and any form of treatment against the patient's will is a violation of this right.³⁹ Moreover the right to privacy grants sexual and reproductive rights.⁴⁰

Information Privacy

One type of privacy also protected under the European right to privacy rules is the information privacy, which is explicitly guaranteed by Art. 8 para. 1 CFR as well as Art. 16 para. 1 TFEU (“Everyone has the right to the protection of personal data concerning him or her”) as well as by Art. 8 ECHR. The right to protection of personal (medical) data is of paramount importance for the assessment of health technologies, which is reflected in the even more specific Art. 10 of the “Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human and Biomedicine” of the Council of Europe⁴¹ which states that everyone has the right to respect for private life in relation to information about his or her health, including the right to know any information collected about his or her health which in turn contains the right of not being informed about his or her own health. The exercise of the latter rights however can be restricted by law if this is in the interest of the patient.

Based on the TFEU the Data Protection Directive 95/46/EC has been enacted which provides more detailed provisions on privacy. Art. 8 para. 1 of the directive obliges the states to “prohibit the processing of [...] data concerning health or sex life”. An exception to this gene-

³⁷ See Case C-44/79 – Hauer – OJ 1979-3727, Case C-540/03 – OJ 2006, I-5769.

³⁸ Art. 8 ECHR uses the older term „correspondence“ instead of „communication“, the latter being more suitable for telecommunication.

³⁹ See for example the judgements of the European Court on Human Rights (ECtHR) *Y.F. v Turkey*, Application no. 24209/94, 22. July 2003 and *Storck v Germany*, Application no. 61603/00, 16. June 2005.

⁴⁰ See for example *S.H. and Others v. Austria*, Application no. 57813/00, ECtHR 03. November 2011.

⁴¹ See below, Research and Development.

ral prohibition can only be justified in the cases of the following paragraphs (for example if the patient has given the consent, para. 2 letter a) of which para. 3 is designed for the context of medical treatment: processing of data is allowed if required for

- F. the purpose of preventive medicine, medical diagnosis, the provision of care or treatment or the management of health-care services, AND
- G. where those data are processed by a health professional subject under national law or rules established by national competent bodies to the obligation of professional secrecy or by another person also subject to an equivalent obligation of secrecy.

The term Privacy contains many individual rights concerning health care and health technologies, ranging from the right of integrity of the body to protection of health related data. Therefore the right potentially gets affected by every health technology, might it be a socio-cultural intervention in which the data protection is of paramount importance, might it be an invasive medical device which affects the integrity of the body. Privacy issues therefore should be considered in every HTA. Important Europe-wide sources to be considered are:

- Art. 7 and Art. 8 Charter of Fundamental Rights,
- Art. 8 European Convention on Human Rights,
- Art. 10 Convention on Human Rights and Biomedicine,
- Data Protection Directive 95/46/EC (see national legislation based on the Directive).

9.3.2 Specifications concerning the technology

On the basis of its competence in Art. 114 TFEU on creating and sustaining the “internal market” for example by regulating competition and free movement of goods and services, the EU has regulated medical devices and pharmaceutical products since the 1960s (Barnard/Peers, 2014, p. 639). The following remarks concern these two types of technologies. The EU-regulation regards every stage of the life cycle of a product: Research and development, marketing and post-marketing (Bache/Flear/Hervey, 2013, p. 12). Many European-wide provision equally concern both,

pharmaceuticals and medical devices, the authorisation however differs substantially which is why it will be explained separately.

Research and Development

Research and development of health technologies for use on humans contains and legally requires clinical trials which are regulated by convention law as well as community law. Based on the ECHR the Council of Europe drafted the first international legally binding convention on biomedical research in 1997, the Convention on Human Rights and Biomedicine also referred to as the Oviedo Convention (Simonsen, 2012, p.4).⁴² The Convention has been amended in 2005 by the Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research which elaborates on the provisions on research, which can be found in Chapter V of the Convention. As a general rule Art. 15 of the Convention and Art. 4 of the Protocol state that all medicinal scientific research shall be carried out freely and according to the appropriate provisions ensuring the protection of the human being. The Convention then defines certain conditions under which research on humans may be undertaken in Art. 16. These include the lack of a comparably effective research possibility, proportionality of potential risks to benefits as well as the informed consent of the proband⁴³. If research is undertaken on persons unable to consent the special conditions of Art. 17 have to be met, e.g. that the results of the research have the potential to produce real and direct benefit to the health of the test person. The Protocol comprises specification for example concerning the examination by an ethics committee in chapter III, information to be given to the probands before the research in chapter IV, as well as provisions for specific situations such as research during pregnancy and breastfeeding (Art. 18).

Furthermore, medicinal research conducted within the EU or conducted outside but used for products that shall be introduced into the European market has to meet the standards of the Clinical Trial Directive 2001/20/EC as well as the Good Clinical Practice Directive 2005/28/EC. According to Art. 1 Clinical Trial Directive this directive applies to all interventional clinical trials and covers provisions concerning for example the protection of clinical trial subjects, especially on minors (Art. 3 and Art. 4), the Commission's detailed guidance on application and documentation of trials (Art. 8)⁴⁴, the need for and work of Ethics Committees (Art. 6 seq.) suspension of the

⁴² The full title of the convention is Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine.

⁴³ For the later see above, Privacy.

⁴⁴ See The rules governing medicinal products in the European Union", Vol. 10 for the guidances, download under: http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm for the guidances

trial or infringements (Art. 12) as well as the manufacturing or importation of investigational medicinal products (Art. 13). The GCP-Directive concerns only trials in which such investigational medicinal products (IMPs) are used. These are defined by Art. 2 (d) Clinical Trial Directive as pharmaceutical forms of an active substance or placebo being tested or used as a reference in a clinical trial.⁴⁵ The directives mainly develops the provisions on the authorisation of manufacturing or importing IMPs (Art. 9 – Art. 15) and procedures of documentation (Art. 16 – Art. 20) and Inspection (Art. 21ff.).

Laboratory trials above all have to be in compliance with the Good Laboratory Practice (GLP) regulated by Directive 2004/10/EC. The Directive obliges Member States to provide legal provisions to ensure that laboratories conducting studies on chemical products meet the GLP standards developed by the OECD and incorporated by the Directive in Annex I. Procedural specifications on monitoring, inspection and verification of GLP by national authorities as well as on reporting standards can be found in Directive 2004/9/EC. The standards to be met by the obliged parties are laid down in Annex I of the Directive.

Depending on the kind of technology to be tested in interventional clinical trials a number of international and community provisions have to be considered. As the compliance of these standards is most always a crucial condition for the authorisation of a technology, they have to be taken into account before the commencement of any trial. Europe-wide legal sources to be factored in an HTA are:

- ▶ Convention on Human Rights and Biomedicine,
- ▶ Clinical Trial Directive 2001/20/EC,
- ▶ Good Clinical Practice 2005/28/EC,
- ▶ Good Laboratory Practice Directive 2004/10/EC,
- ▶ Directive on Inspection and Verification of GLP 2004/9/EC (see national legislation based on all Directives).

Intellectual Property

The protection of intellectual property is extensively regulated by the EU. The regime of the European Patent Convention (EPC) allows for the granting of European patents through a harmonised procedure in front of the

European Patent Office (EPO). Object of such patent can be any invention, in all fields of technology that is new (see Art. 54), based on an inventive step (see Art. 56) and is susceptible of industrial application (see Art. 57). Most medical devices as well as pharmaceuticals are patentable according to the rule if they feature the said characteristics (Podbielski, 2012, rec 74). Besides the general exclusion of any inventions the commercial use of which would be against the “ordre public” in Art. 53 letter a), letter c) explicitly suspends methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body from patentability. This, however does not apply to the used products and substances used in the method as Art 53 letter c), 2nd sentence states. The differentiation between method and used product can be difficult and crucial and should be supervised by legal experts in case of uncertainty.⁴⁶ The patent can be granted for 20 years in those Contracting States of the EPC named in the application according to Art. 79 EPC. In each Contract State in respect to which it granted, the patent confers the same rights as would be conceded by a national patent in that state, Art. 64.

For the protection of intellectual property on pharmaceutical products another instrument exists, the so called supplementary protection certificate for medicinal products normed in the Regulation (EC) No 469/2009⁴⁷. However, this certificate is accessory to an existing patent which is “extended” by the certificate, Art. 4. According to Art. 9 of the regulation the application for any extensions of the basic patent shall be addressed to the competent office that granted the basic patent. In the case of paediatric pharmaceuticals the protection by a patent or a supplementary certificate can be prolonged by six month.⁴⁸

In the area of biotechnology and genetic engineering yet another directive has to be considered, the Directive 98/44/EC on the legal protection of biotechnological inventions. The Directive, allowing for the increasing importance of biotechnology⁴⁹, obliges the Member States to protect biotechnological inventions under national patent law. Exceptions to this general rule under Art. 5 and Art. 6 that are of specific concern for health care, are the human body, at the various stages of its formation and development as well as such inventions which are in contrary to the “ordre public”, such as processes for cloning human beings, modifying the germ line genetic identity of human beings and so forth.

⁴⁵ For more concrete information on the so called IMPs, see the Commissions definition in The rules governing medicinal products in the European Union”, Vol. 10, Chapter 5, download under: http://ec.europa.eu/health/documents/eudralex/index_en.htm.

⁴⁶ See for example case T 0426/89 of 28. June 1990 in front of by the Boards of Appeal at EPO. The Boards decided the use of a cardiac pacemaker for the treatment of tachycardia is not patentable while the specific construction of such a pacemaker can be patentable.

⁴⁷ The novel version of the older and often changed Reg. (EEC) No 1768/92.

⁴⁸ See Art. 36 of Regulation (EC) No 1901/2006 on medicinal products for paediatric use and the amending Regulation (EC) No 1902/2006.

⁴⁹ See No (1) of the Recitals, Directive 98/44/EC.

Although the question of intellectual property might often be solved before an HTA is conducted, it should be ensured that all necessary measures have been taken. Important Europe-wide legal sources to be considered are:

- ▶ European Patent Convention (if a European patent is desired/national patents not sufficient),
- ▶ Regulation concerning the supplementary protection certificate for medicinal products (EC) No 469/2009,
- ▶ Regulation on medicinal products for paediatric use (EC) No 1901/2006,
- ▶ Directive on the legal protection of biotechnological inventions 98/44/EC (see national legislation based on the Directive).

Authorisation

In the case of medicinal products and medical devices the question of authorisation is paramount. The legal question of authorisation by the competent body is special in two ways: first it is closely linked to other parts of the HTA as for example the clinical innocuousness of a drug is a necessary condition for getting authorisation. Furthermore, authorisation of medicinal products as well as medical devices is exhaustively regulated on the EU level. For further details on the authorisation process one has to distinguish between medical and pharmaceutical products both of which are regulated by different directives. The differentiation can be made upon the provisions of Art. 1 lit. a) Medical device directive (MDD) 93/42/EEC:

“‘medical device’ means any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:

- ▶ diagnosis, prevention, monitoring, treatment or alleviation of disease,
- ▶ diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- ▶ investigation, replacement or modification of the anatomy or of a physiological process,
- ▶ control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means”.

Accordingly, a medical device has to be an article that serves one of the specified purposes and does so by mechanical, physical or chemical-physical means and not by a pharmacological, immunological, or metabolic reaction. Medicinal products in contrast work explicitly in the latter stated ways; Art. 1 Directive on medicinal products for human use, 2001/83/EC defines medicinal products as:

“(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or

(b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.”

According to this definition medicinal products are basically what can be called a drug, medicine, or pharmaceutical. Medical devices on the other hand are for example blood-bags, cochlea-implants, injection-needles, operation-tables and so forth. However a clear general definition of both terms is not possible, a case by case consideration therefore indispensable. Borderline cases are for example medical products that contain medicinal products, such as bone-cement with antibiotics or heparin coated catheters.

Furthermore, medical devices are subdivided into In vitro diagnostics, active implantable medical devices and ‘normal’, i.e. all other medical devices, each of which regulated in a different directive: In vitro diagnostics directive (IVDD) 98/79/EC, active implantable medical device directive (AIMDD) 90/358/EEC and the already mentioned MDD. These different types of medical devices can also cause borderline problems for example bone anchored hearing aids (not cochlea implants) for which the implantable component is non active while the active component is not implanted (such devices are fall under the MDD 93/42/EEC for the AIMDD requires the activity of all vital implantable parts of the device). Other distinctions such as between medical devices and cosmetic products or biocides can also be problematic. In cases in which the definition of the technology in question, the European Commission’s website on reference documents and the guidance MEDDEVs can be very helpful: http://ec.europa.eu/growth/sectors/medical-devices/documents/index_en.htm. It has to be recognised however that these guidelines are not legally binding and no legal claim can be constituted on these. Moreover it should be stated that products can fall under different

directives, if they fulfil all characteristics. On this, also notice the provision in Art. 2 Nr. 2 Directive 2001/83/EC.

The procedure and requirements of authorisation depend on the elaborated distinction:

Medical Devices, in vitro diagnostic medical devices, active implantable medical devices

Medical devices can be authorised for the EU if they comply with the so-called 'essential requirements' according to Art. 3 MDD 93/42/EEC which refers to Annex I of the directive. The directive itself however does not contain any technical specifications but Art. 5 MDD refers to harmonised standards (such as EN, ISO, DIN etc., see http://ec.europa.eu/growth/single-market/european-standards/harmonised-standards/index_en.htm for more information on standards) which are not legally binding. However, application of these standards induces a general presumption of conformity with the essential requirements and can be demonstrated by attaching the CE-sign to the device after assessing conformity in a certain procedure. Which options the manufacturer has to assess conformity of his product depends on the product's class which again results from the provision of Annex IX MDD and according to the risk the device potentially poses on the patient. As the different assessments vary from internal control of conformity by the manufacturer himself (Annex VII MDD) to production or product quality involving an external notified body (Annexes V and VI MDD) up to full quality assurance systems (Annex II) this classification according to Annex IX is crucial and has to be supervised legally. Active implantable medical devices in toto need a conformity process according to class III i.e. the class of highest risk.

Medicinal products

Five different procedures are available for the authorisation of medicinal products within the EU:

1. the National Procedure for authorisation of pharmaceuticals in one Member State;
2. the Mutual Recognition Procedure (MRP) for pharmaceuticals that have authorisation in one Member State which shall be extended to other Member States;
3. the Decentralised Procedure (DCP) for new pharmaceuticals for which authorisation in several Member States is sought;
4. the Centralised Procedure for authorisation of pharmaceuticals for which authorisation in all Member States of the European Union is sought or for which the Centralised Procedure is mandatory;
5. the Parallel Import Licence for authorisation of pharmaceuticals that have no central authorisation, are imported into one Member State to another and distributed outside the distribution channels and are sufficiently similar to the pharmaceutical authorised in the questionable Member State (this shall not be subject of this guidance, see the Commission Communication on parallel imports of proprietary medicinal products for which marketing authorisations have already been granted (COM(2003) 839) for more information: <http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52003DC0839>).

Competent body for the National Procedure is the national agency for drug safety, for example Medicines and Healthcare Products Regulatory Agency (MHRA) in Great Britain or Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) in Germany. These national agencies are also the competent bodies for MRP and DCP. In both procedures one Member State has to be designated as Reference Member State (RMS) responsible for executing the procedure. In Case of MRP the Member State in which marketing authorisation has been granted already is automatically the RMS. Obligation of the RMS is to prepare an assessment report within 120 days after the application in DCP respectively 90 days in MRP. Moreover the RMS's agency supports the applicant in preparation of the application to all concerned Member States. The Concerned Member States (CMS) are given the opportunity to comment on the assessment report and other documents such as the package insert and labels within 90 days. If a CMS claims that the pharmaceutical poses a serious risk to public health, the Coordination Group for Mutual Recognition Procedures and Decentralised Procedures – Human (CMDh) works toward a consent about the product in question. If consent cannot be reached, the case is solved by the Committee for Human Medicinal Products (CHMP) in an arbitration procedure. Mutual Recognition Procedure and Decentralised Procedure are both regulated in Art. 28 seqq. of the Directive 2001/83/EC on the Community code relating to medicinal products for human use. More detailed information on these procedures can be found in Vol. 2 The rules governing medicinal products in the European Union, Chapter 2:

http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm.

The Centralised Procedure is possible for every pharmaceutical for which market authorisation is sought for the whole European Union. For some medicinal

products it is even mandatory – the other procedures are not available for these certain products. The Centralised Procedure is regulated in the Regulation (EC) No 726/2004 on Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. Annex I of the regulation names three groups of pharmaceutical products that have to be authorised centrally:

- ▶ Products that are produced by means of recombinant DNA technology, controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells, hybridoma and monoclonal antibody methods.
- ▶ Products that contain a new active substance that has not been authorised before 2004 and meant to treat acquired immune deficiency syndrome, cancer, neurodegenerative disorder, diabetes, autoimmune diseases and other immune dysfunctions, or viral diseases.
- ▶ Medicinal products that are designated as orphan medicinal products pursuant to Regulation (EC) No 141/2000.

The application for a Centralised Procedure has to be directed to the European Medicines Agency (EMA). The assessment of the pharmaceutical concerning its quality, safety and efficacy is conducted by the Committee for Human Medicinal Products (CHMP) which consists of scientists delegated by the national agencies. The positive or negative decision of the committee is taken as a basis for the decision of the European Commission which eventually authorises the product when indicated. More detailed information about the Centralised Procedure can be found in Vol. 2 The rules governing medicinal products in the European Union, Chapter 5 and 6: http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm.

The analytical, pharmacotoxicological and clinical standards for testing the quality, efficacy and safety of medicinal product can be found in Directive 2001/83/EC, Annex I and are structured according to the guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). These standards are substantiated by non-binding guidelines of the EMA, which can be found online (<http://www.ema.europa.eu/>).

The question of authorisation can be seen as paramount for all medical devices and medicinal products.

The procedures and requirements for authorisation are diverse and have to be supervised legally. However, not every technology subject to an HTA includes the use of a medical device or pharmaceutical product that has not been authorised yet. Both the national agencies, as well as the European Medicines Agency offer databases in which authorised products are enlisted. Important Europe-wide legal sources to be considered are:

- ▶ Directive 98/79/EC for in vitro diagnostics,
- ▶ Directive 90/358/EEC for active implantable medical devices,
- ▶ Directive 93/42/EEC for all other medical devices,
- ▶ Directive 2001/83/EC for the Decentralised and Mutual Recognition Procedure for the authorisation of pharmaceuticals, and
- ▶ Regulation (EC) No 726/2004 for the Centralised Procedure for the authorisation of pharmaceuticals.

9.3.3 References

- BACHE, G., FLEAR, M.L., HERVEY, T.K. (2013) The defining features of the European Union's Approach to Regulating New Health Technologies. In: Flear, M.L., Hervey, T.K., Farrel, A-M., Murphy, T. (eds.) *European Law and New Health Technologies*. Oxford: Oxford University Press.
- BARNARD, C., PEERS, S. (eds.) (2014) *European Union Law*. Oxford: Oxford University Press.
- BUCHNER, B. Privacy. In: BUIJSEN, M., DEN EXTER, A. (eds.), *Compendium on European Health Law* [to be published in 2015].
- CHALMERS, D., DAVIES, G., MONTI, G. (2014) *European Union Law*, 3rd Ed., Cambridge, Cambridge University Press
- PODBIELSKI, Y. (2012) Art 53. In: Singer, R., Stauder, M. (eds.) *Europäisches Patentüberinkommen – Kommentar*. Köln: Karl Heymanns.
- SIMONSEN, S. (2012) *Acceptable Risk in Biomedical Research – European Perspectives*, Heidelberg/London: Springer.
- WARREN, S., BRANDEIS, L. (1890) The Right to Privacy, *Harvard Law Review*, 4, 193.
- TAMARAK, K.H., MCHALE, J.V. (2004) *Health Law and the European Union*. Cambridge: Cambridge University Press.

- 1 Integrated health technology assessment for evaluating complex technologies (INTEGRATE-HTA):
An introduction to the guidances
- 2 Guidance on the integrated assessment of complex health technologies – The INTEGRATE-HTA Model
- 3
- 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
- 6 Guidance on the use of logic models in health technology assessments of complex interventions
- 7
- 7 Guidance on choosing qualitative evidence synthesis methods for use in health technology assessments of complex intervention
- 8
- 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



This project is co-funded by the European Union under the Seventh Framework Programme (Grant Agreement No. 306141)