ETHICAL EVALUATION IN HEALTH TECHNOLOGY ASSESSMENT

DEVELOPMENT OF A PROCEDURAL FRAMEWORK FOR INCORPORATION OF ETHICAL CONSIDERATIONS IN HEALTH TECHNOLOGY ASSESSMENT

By

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A Thesis Submitted to the School of Graduate Studies in Partial Fulfillment of the Requirements for the Degree Doctor of Philosophy

DESCRIPTIVE NOTE

Doctor of Philosophy (2016) McMaster University

Faculty of Health Sciences, Department of Clinical Epidemiology and Biostatistics:

Health Research Methodology – Health Technology Assessment

TITLE: Development of a Procedural Framework for Incorporation of Ethical

Considerations in Health Technology Assessment

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NUMBER OF PAGES: xi, 196

ABSTRACT

Background and objectives

Addressing ethical issues in health technology assessment (HTA) can increase transparency and accountability of the HTA process and lead to better-informed healthcare decisions. Despite its importance, integration of ethics into HTA remains challenging. The objective of this thesis was to develop a process-based framework to support ethical evaluations in HTA and increase their applicability.

Methods

Project 1: A systematic literature review was conducted with the purpose of identifying and mapping the methodological features of the existing frameworks for ethics in HTA.

Project 2: A systematic literature review and an international survey of HTA agencies were conducted to explore how ethical evaluations may be encouraged or discouraged in the HTA practice.

Project 3: A procedural framework was drafted based on the operational features of the identified guidance documents as well as barriers and facilitators for incorporating ethics into HTA.

Project 4: The framework was applied to a hypothetical case study, with the aim of helping HTA practitioners touch on key points of the steps outlined by the proposed framework.

Results:

    <u>Project 1</u>: The identified ethical frameworks vary in their purpose, philosophical approach, structure, and comprehensiveness. The review results suggest that the choice of a method for collection and analysis of ethical data depends on the context, purpose of analysis, and availability of resources.

    <u>Project 2</u>: The results of this study emphasize the importance of simplification of ethics methodology and development of good practice guidelines in HTA, as well as capacity-building for engaging HTA practitioners in ethical analyses.

    <u>Project 3</u>: The proposed framework consists of an algorithmic flowchart, showing different steps of an ethical evaluation throughout the HTA process; a stepwise guide, which focuses on the tasks and potential questions that are required to be addressed at each step; and a list of some commonly recommended tools to facilitate the evaluation process.

    <u>Project 4</u>: The case study outlines the key tasks, recommended by the framework, and provides examples of process outputs that could be considered when attempting to perform an ethical evaluation.

Conclusions:

The outputs of this thesis can be used to support and promote a more consistent practice of ethical evaluation among HTA professionals. However, further validation of the proposed framework is required to establish its utility for HTA practice.

PREFACE

This thesis is a "sandwich thesis" consisting of four individual projects prepared for

publication in peer-reviewed journals. Two of the papers are published, one is in

submission, and the forth paper will be submitted to a peer-reviewed journal. The

contributions of Nazila Assasi to all of the papers in this thesis include: developing the

research ideas and research questions, collecting the required data, performing the

analyses, interpreting the results, preparing the manuscripts, submitting the manuscripts

for publication, and responding to reviewers' comments. The work in this thesis was

conducted between fall 2011 and fall 2015.

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to my supervisor, Dr. Lisa Schwartz, and the members of my thesis supervisory committee, Dr. Daria O'Reilly and Dr. Jean-Eric Tarride, whose guidance throughout and beyond this thesis research have been invaluable.

I would also like to extend my gratitude to Ron Goeree for introducing me to health technology assessment, and for his valuable directions and contributions to research provided in this thesis. I am grateful to Kaitryn Campbell for her assistance with the literature searches and to Ken Bond for providing insightful comments on Chapter 5 of the thesis.

Last but certainly not least, I would like to thank my immensely supportive family, specifically my husband Hamid Jamali, and our daughter Narges. There are no words to convey how much I appreciate their love and constant support.

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LIST OF ABBREVIATIONS

CADTH   Canadian Agency for Drugs and Technologies in Health

CRC   Colorectal Cancer

dMMR   Mismatch Repair Deficiency

DAHTA   German Agency for Health Technology Assessment

EUnetHTA   European Network for Health Technology Assessment

INAHTA   International Network of Agencies for Health Technology Assessment

LS   Lynch Syndrome

MSI   Microsatellite Instability

NICE   National Institute for Health and Care Excellence

SBU   Swedish Council on Health Technology Assessment

WHO   World Health Organization

WRE   Wide Reflective Equilibrium

CHAPTER 1

Thesis Introduction

HTA is a multidisciplinary process that aims to inform health technology-related

decisions at the practice, management, and policy-making levels in the healthcare system

(1). This is usually done through a comprehensive evaluation of clinical, social, legal,

ethical, and economic implications of the introduction, development and implementation

of a health technology (drugs, programs, medical devices, surgical interventions, etc.) (2).

As a result, HTA has increasingly been considered as an influential tool for informing

priority-setting, reducing decision uncertainties, and facilitating resource allocation (3).

Healthcare technologies may be associated with ethical controversies and challenges that

create uncertainties and confusion as to what decisions ought to be made regarding the

implementation of the technology.(4) One frequently cited example of technologies

around which ethical controversies exist is cochlear implants for deaf children. A

cochlear implant is an assistive hearing device designed to restore sound perception in

those suffering from moderate to profound hearing impairment. The device is surgically

placed in the inner ear and stimulates the auditory nerve with electrical signals (5).

Cochlear implants are reported to have beneficial effects, based on audiological criteria,

on restoring partial hearing in deaf children(5), and their use for young children has been

endorsed by several administrative and professional associations (6-10). However, there

exists an extensive amount of ethical literature arguing for and against this type of

hearing aid device. Proponents of cochlear implants claim that severe hearing loss

negatively impacts the social and educational competence of deaf children, and hence,

cochlear implants can improve their psychological and overall wellbeing (5;11;12).

Advocates argue that cochlear implants not only provide deaf children with the benefit of

hearing, but also enables them to participate in society in a more equitable manner (13).

Therefore, they suggest that it is a moral obligation for the parents and society to ensure

that a deaf child receives a cochlear implant as early as possible (5;12). On the other

hand, opponents of cochlear implants argue that deaf children are less likely to benefit

from this type of device, referring to the wide variation in its reported success rates, and

the fact that cochlear implants are not able to restore normal hearing (13-15). They also

propose significant arguments based on ethical principles, values, and cultural factors,

some of the most important ones being: side effects of cochlear implantation (e.g., device

failure, need for repeated surgeries, and increased risk of meningitis); increased risk of

psychosocial problems (e.g., anger and violence due to misunderstanding, and personality

or self-image problems); concerns about right of self-determination (i.e., parents making

surrogate decisions for their children); and concerns about cultural rights (i.e., failure to

acknowledge deaf culture, and elimination of its cultural resources), as well as linguistic

rights (i.e., preventing deaf children from acquiring accessible (sign) language during the

early years of life) (14-18).

With this example in mind, it appears evident that HTAs can be less useful for decision-

making if they fail to represent ethical values and other normative aspects which may

have an impact on the implementation and utilization of new healthcare technologies (19). However, despite the increasing recognition of the importance of ethical evaluation as a part of the HTA process (4;20;21), ethical considerations around technologies are usually neglected or poorly addressed in the majority of HTA reports (22-24). This PhD thesis aims to fill in this gap by developing a framework to support ethical evaluations in HTA projects.

The remainder of this chapter provides an explanation of what the term "ethics" refers to and how it is highly relevant to HTA, and vice versa; some arguments as to why ethical issues are frequently neglected in the current practice of HTA and what drawbacks might be associated with ignoring or inadequately dealing with ethical issues around healthcare technologies; a discussion about the benefits of having a structured framework for the evaluation of ethical aspects in HTA and the rationale for the development of an action-oriented framework; followed by the thesis objectives; and a brief outline of the thesis chapters.

Ethics and its place in HTA and vice versa

Ethics is a broad term used to describe a branch of philosophy that deals with values and addresses varying moral questions of acceptable and unacceptable human conduct. It is defined by Merriam-Webster's dictionary as "an area of study that deals with ideas about what is good and bad behavior" and as "a branch of philosophy dealing with what is morally right or wrong" (25).

Ethics, as a normative endeavour, is different from empirical science in the sense that unlike the empirical sciences which aim to describe the facts, ethics is concerned with values and attempts to discuss the ways in which things ought to be (26). Bioethics is defined as "the systematic study of human conduct in the area of the life sciences and health care" and it is usually examined based on moral values, principles and rules (26). Ethical evaluation of biotechnologies, at individual, public or policy-making levels, can then be regarded as a part of bioethics.

Ethics has a place in every stage of the HTA process, from selection of a technology for assessment through data collection and analysis to decision-making based on the assessment results. A number of reasons have been proposed in support of ethics as a distinct domain in HTA. As with all technologies, healthcare technologies have embedded values and moral properties that can influence or challenge the moral values of individuals or society (27). In addition, choosing between technological options can be controversial (4). Examples of ethical controversies around healthcare technologies are those around risks and benefits of developing or using a technology (e.g., treatment effect, adverse events, mortality), efficiency and equity (e.g., unjustified privileges or disadvantages to particular social or cultural groups), power and control over the technology (e.g., freedom of choice, informed consent), changing the concept and value of life (e.g., cloning technologies, euthanasia), and changing human relationships (e.g., surrogate motherhood). Technologies may give rise to previously unknown ethical

problems (e.g., human genetic engineering) or unexpected ethical controversies (e.g., abortion based on genetic predictive tests, and cochlear implants). They can also alter the human ability to control and transform nature (e.g., genetic engineering and cloning technologies). Finally, ethical evaluation can serve as a basis for public involvement and inquiry about values and preferences of stakeholders (28-30).

Thus, for all of the above reasons, ethical evaluations are needed in HTA to provide a more detailed understanding of potential uncertainties, complexities and public preferences surrounding healthcare technologies. Furthermore, methods used in HTA should be ethically sound. HTA, as a process, has been argued to be value-laden due to normative assumptions and value choices involved in the process (31).

HTA has a place in ethics as a method and procedure for informing healthcare decision-making and ultimately improving the wellbeing of individuals and society. Any move toward a flawless evaluation of healthcare technologies can serve as an ethical practice. In addition, since HTAs are of instrumental value in enhancing transparency and accountability of decision-making, they can be considered as an ethical activity where decision-makers need to be reasonably certain of the fairness of their policy decisions (32). Many different frameworks that focus on procedural criteria needed for a fair healthcare decision-making can be found in the literature (33). A highly regarded ethical framework for fair and legitimate priority-setting, suggested by Daniels and Sabin, argues that a fair healthcare system is one in which there is accountability for reasonableness

(30). According to this procedural framework, decisions about healthcare technologies should be made based on: relevance (evidence, reasons and principles that are acceptable for "fair-minded" people), publicity (transparency and openness), revisions and appeals (opportunities to challenge and revise decisions based on further evidence or stakeholder feedback), and reinforcement (public regulation to ensure the first three conditions are fulfilled). To support a framework such as accountability for reasonableness, HTA must take account how technical, ethical and social concerns are defined and transparently describe value judgements around healthcare technologies (34). Other scholars have argued that, although the procedural criteria proposed by Daniels and Sabin might be necessary for the permissibility of health policy decisions, they are not sufficient (35-37). For example, Gibson *et al.* suggested "empowerment" as a fifth criterion, arguing that power differences should be minimized in the decision-making context and opportunities should be created for effective participation in priority setting (37). Therefore, it is arguable that the HTA process should enable stakeholders and the public to establish what would count as fair decision-making and accountability for policies. According to Reuzel *et al.*, HTA can be considered as, "an inquiry into the value of a technology for those who are affected by subsequent decisions, i.e., the persons involved" (38). Therefore, the usefulness of HTA results for policy making should not only be evaluated in terms of whether they incorporate ethical and other normative aspects in the assessment, but in the form of public participation to establish the relevance, adequacy and acceptability of HTA results from potential stakeholders and the public's viewpoints.

Neglecting ethics in HTA: reasons and potential consequences

The notable lack of ethical evaluations in published HTA reports (22-24) indicates a possible reluctance of HTA producers to include ethical considerations as part of their assessments. There are several reasons why ethics has not been sufficiently addressed in HTA practice (39). One of the commonly cited arguments is that there are significant methodological differences between ethics and empirical science. Methods used to address clinical and economic aspects of healthcare technologies, for example, focus on unbiased estimations of outcomes for implementing or utilizing a technology. An ethical analysis, on the other hand, tends to look for moral values and dilemmas around the technology, and uses philosophical theories to justify certain reasons for the implementation of a technology or otherwise. Therefore, different approaches must be used to tackle ethical issues, in which HTA practitioners may not necessarily have specialized knowledge and skills. What adds to this problem is the lack of a commonly agreed-upon ethical evaluation methodology in HTA.

Another essential problem is that ethical approaches might often be considered to be insufficient to cover specific normative issues around healthcare technologies, such as political pressure on screening programs or vaccines; or to address technology-related issues that are important for decision-making. (39) In addition, ethics has been anecdotally suggested to be associated with the possibility of unnecessary disagreements during the decision-making process. Therefore, performing ethical evaluation, in some organizations, may appear to be an activity the importance of which should be viewed in

light of its opportunity cost, which is the opportunity forgone by spending time on issues which may not be used by decision-makers.(40)

The reluctance of HTA-producers to incorporate ethics in their assessments can also stem from the belief that ethical reflection is only necessary for morally challenging technologies (e.g., genetic testing technologies), or only when clarification is needed on some moral issues for the purpose of decision-making. In spite of the fact that ethical analysis may be better suited to some technological areas than others, ethical evaluation seems to be necessary for the assessment of all categories of healthcare technologies, as every type of technology may be subject to a range of uncertainties as well as unknown social or ethical impacts.

Some HTA producers support evaluation of ethical aspects of technologies, but not necessarily as one of their primary responsibilities (39). They may simply believe that the evaluation of ethical aspects does not concern them and, therefore, assign this responsibility to other sectors of authority or research. Others suggest that ethical evaluation methods do not offer an adequate basis for addressing important ethical aspects of healthcare technologies. As a result, they tend to use technical and empirical reasoning methodologies to deal with ethical issues. For example, discussions around a number of technological ethical dilemmas (such as access, equity, acceptability, etc.) might often be presented in the form cost-effectiveness (e.g., cost-utility or cost-benefit) analyses. It is arguable that although these methods can usefully describe some ethical

problems (e.g., equity concerns) or societal preferences, they are usually unable to provide sufficient ethical justifications that can be used as a foundation for decision-making. In addition, these types of analyses are dependent on methodological choices and assumptions, which themselves are subject to value judgements (31).

Another possible, but less frequently recognized, reason for not performing an ethical evaluation in HTA is what has been referred to as 'acceptabilism' (41). This concept is used when one considers social or political authorization as equivalents to ethical evaluation. There seems to be a growing tendency for explicitly using public and stakeholder engagement strategies in order to address social and ethical issues around healthcare decisions. It is needless to argue that the act of engaging the public in HTA is a democratic act and has moral value. The more an HTA process involves the public and stakeholders in the assessment, the more accountable the HTA results will be in representing societal values and giving a voice to otherwise neglected groups. However, participatory approaches should be seen not as a substitute for ethical analysis, but rather as a complementary method to moral reasoning (38).

In summary, ethics makes an important contribution to the fair and sound assessment of healthcare technologies. Incorporation of ethics and other normative aspects in the HTA process can help decision-makers to ensure that all relevant dimensions of decision making are sufficiently considered. They can thus communicate a more robust rationale for their decisions. The first direct consequence of neglecting ethical considerations in

HTA would be leaving healthcare policy-makers with decision uncertainties. To address this concern, Lehoux and Williams-Jones argue that in order to provide policy-makers with a firmer basis for decision making, HTA organizations have a professional obligation to conduct comprehensive assessments that include social and ethical aspects of technologies (42). On the other hand, since the ultimate goal of developing healthcare technologies is to improve people's health, ignoring ethical implications in HTA can clearly be in conflict with the moral obligation of the healthcare system to fulfill the duty of care to patient and the public (4).

For the above-mentioned reasons and consequences, ethical implications of healthcare technologies are increasingly being recognized as part of a standard HTA process. To optimize evaluation of ethical considerations in HTA, a number of scholars and HTA organizations have turned their attention to developing guidance documents that are more comprehensive in their scope and more specific in their methods (43). However, despite these efforts, ethical evaluation has largely failed to become embedded as a part of routine HTA practice (44). This knowledge-to-practice gap has led to calls for the development of ethical frameworks that are more adaptable and user-friendly (45). This was the primary motivation behind the current thesis project, which will be explained in the next section.

Benefits of a structured framework for ethical evaluation in HTA

The rationale for this thesis centers on the lack of a practical framework that focuses on the process of ethical evaluation in routine practice of HTA rather than informing how ideally ethical evaluations ought to be performed. Although it is generally agreed that an effective ethical evaluation needs to rely on appropriate procedures and methods, operational guidance remains quite limited in the majority of formal guidelines proposed for the evaluation of ethics in HTA (39). Focusing on this gap, it was decided that a means of constructing a systematic, action-oriented framework needed to be developed. Using a 'systematic' and 'action-oriented' framework for ethical evaluation has the following advantages:

1) Ethical evaluation is usually understood as a normative process which requires consideration of not only the factual consequences of implementing or not implementing a candidate technology, but also the underlying values and preferences upon which a decision should be based (Figure 1). Hence, adding ethical evaluation activities to routine HTA practice may tend to increase the complexity of carrying out an HTA process. Therefore, establishing a systematic action-oriented approach to ethical evaluation can help HTA-producers to conduct optimal assessments by reducing the risk of neglecting important methodological steps.

2) The incorporation of ethics in HTA cannot happen in isolation. Ethics is closely connected to cultural, social and legal concerns. At the same time, the results of

clinical and economic assessments may affect the evaluation of ethical concerns by promoting moral arguments, for instance, over certain safety or equity concerns (Figure 1). All of these aspects can be appropriately correlated when an evaluation is carried out in a systematic manner.

3) An action-oriented framework can promote a better understanding among HTA practitioners and professionals about a comprehensive ethical evaluation, and sensitize them to the importance of ethical concerns in their assessments.

4) A systematic framework can enhance the transparency and consistency of the evaluation process, and lead to higher acceptability and credibility of the ethical evaluation results by the end-users (e.g., decision makers).

5) Such a framework allows for accountability and quality assurance because it enables managers and evaluators of the ethical evaluation process to check whether the relevant methodological steps have been completed. It can also serve as a basis for the development of training material for HTA professionals.

Thesis objectives:

To promote routine incorporation of ethical considerations in HTA, this thesis research aimed to develop a process-based framework to support ethical evaluations in HTA and

increase their applicability. More specific objectives which were formulated to guide different phases of the research are described in the relevant chapters.

Key terms:

Although the terms assessment, evaluation, and appraisal can often be used interchangeably, they can present different aspects of the same concept.(31;46-48) *Assessment* is the process of taking an objective measure of outcomes of a healthcare technology by gathering and summarizing information (e.g., assessment of clinical effectiveness and safety). *Evaluation* takes a step further and assessed a healthcare technology in order to determine its value (e.g., evaluation of economic or ethical aspects). As analytical activities, both *assessment* and *evaluation* can provide decision-makers with objective results. *Appraisal, on the other hand,* is referred to a political process of making a decision about healthcare technologies by combining assessment information with values and other important factors (e.g., organizational considerations).(31;47)

Overview of thesis chapters

This thesis was conducted in multiple phases, each one building on the findings of the previous phase. The overall structure of the thesis is illustrated in Figure 2. The thesis consists of three manuscripts and one case study. Two of the manuscripts (Chapter 2 and Chapter 3) have already been published in peer-reviewed journals (43;49), and one manuscript (Chapter 4) is currently in submission (50).

Chapter 1

This chapter serves as the background to the thesis, as it provides some basic information about HTA and the role of ethics in it. This chapter also frames the research problem by describing some of the challenges associated with incorporation of ethics in HTA, outlines the justification for the thesis research and introduces the study objectives, and links the thesis chapters to each other.

Chapter 2

This chapter provides an overview of the methodological features of existing guidance documents for incorporation of ethics in HTA through a systematic review of the published literature and a systematic search in the websites of HTA agencies throughout the world. The focus of this chapter is on theoretical themes, areas of focus, and methodological approaches for collection, appraisal, synthesis, or interpretation of ethical data. This review classifies previously proposed guidance documents for ethics in HTA based on their methodological features, and identifies a range of approaches and tools which could be used in the development of a framework to aid consideration of ethical issues throughout the HTA process.

The systematic review presented in Chapter 2 has been published in full as a peer-reviewed article in *Expert Review of Pharmacoeconomics and Outcomes Research* (43). Data from this manuscript was also presented at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 19th Annual International

Meeting which was held in Montreal (QC, Canada) in June 2014. The abstract of this poster presentation has been published in *Value in Health* (51).

Chapter 3

With the prior knowledge that ethics have largely failed to become embedded in the routine practice of HTA, this part of the thesis intends to explore requirements of a successful integration of ethics in HTA. Chapter 3 provides the results of two complementary studies that aimed to increase understanding of how ethical evaluations may be encouraged or discouraged in the HTA practice: (a) a systematic review of the literature; and (b) an 18-item online survey that was distributed to 56 HTA agencies affiliated with the International Network of Agencies for Health Technology Assessment. The findings of the literature review and the survey have been published as a peer-reviewed paper in the *International Journal of Technology Assessment in Health Care*.(49) This study provides important insights into the current practice of ethical evaluation across different HTA agencies as well as identifying factors that are likely to challenge or facilitate the ethical evaluation process.

Chapter 4

The motivation for this part of research stems from the belief that only through a structured procedural framework can ethical issues be efficiently addressed in HTA. This chapter describes the methodological approach that was used for the development of a framework to aid ethical evaluation in HTA, followed by an introduction of the suggested

stepwise framework as well as a detailed explanation of the framework. An abstract of

this study was presented at the 2016 CADTH Symposium, which was held in Ottawa in

April 2016, and a full version has been accepted for publication in *BMC Medical Ethics*

(50).

The stepwise framework proposed in Chapter 4 is important in the sense that it structures

the evaluation steps and activities as well as HTA professional's role in the process. This

framework is intended to guide HTA-producers, especially those who are not accustomed

to performing ethical evaluations, and to provide them with a knowledge base that is

necessary for collaborating in the evaluation of ethical issues in HTA. It can also be used

by researchers, evaluators, or decision-makers in order to critically appraise the process

used for ethical evaluation. In addition, the framework is suitable for educational

purposes, especially to show the flow of activities needed for a successful evaluation of

ethical issues.

Chapter 5

As a supplement to Chapter 4 (framework proposal), Chapter 5 uses a hypothetical but

realistic scenario case study example to illustrate how the proposed framework can guide

an ethical evaluation. This case study demonstrates how the framework can be applied in

real life and reveals practical considerations to the application. In addition to a step by

step explanation of evaluation tasks, this chapter also proposes suitable tools, practical

tips, and examples of potential outputs for each step, in order to facilitate the evaluation process.

Chapter 6

This chapter provides an overview of the main findings presented in the thesis and discusses the implications of the study results, followed by a discussion of the strengths and weaknesses of the thesis, conclusions and the directions for future research.
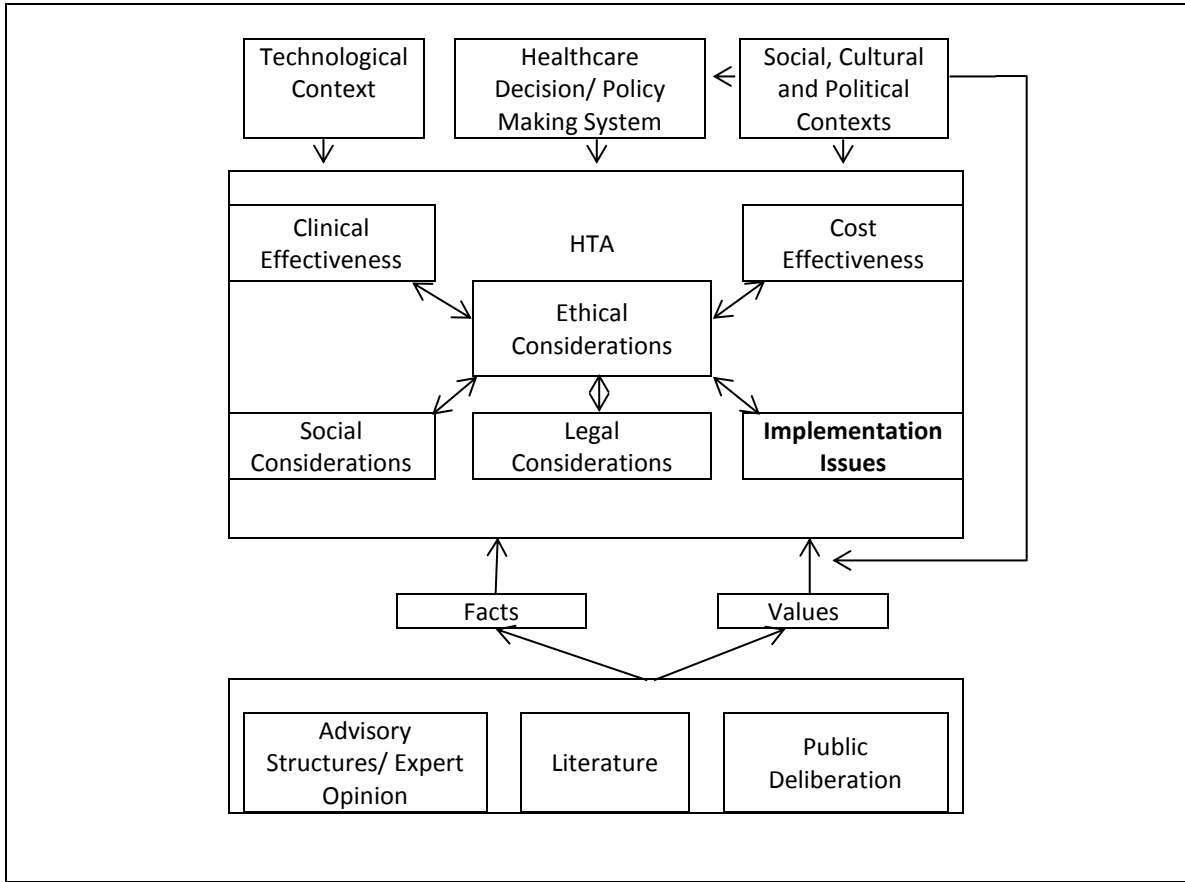
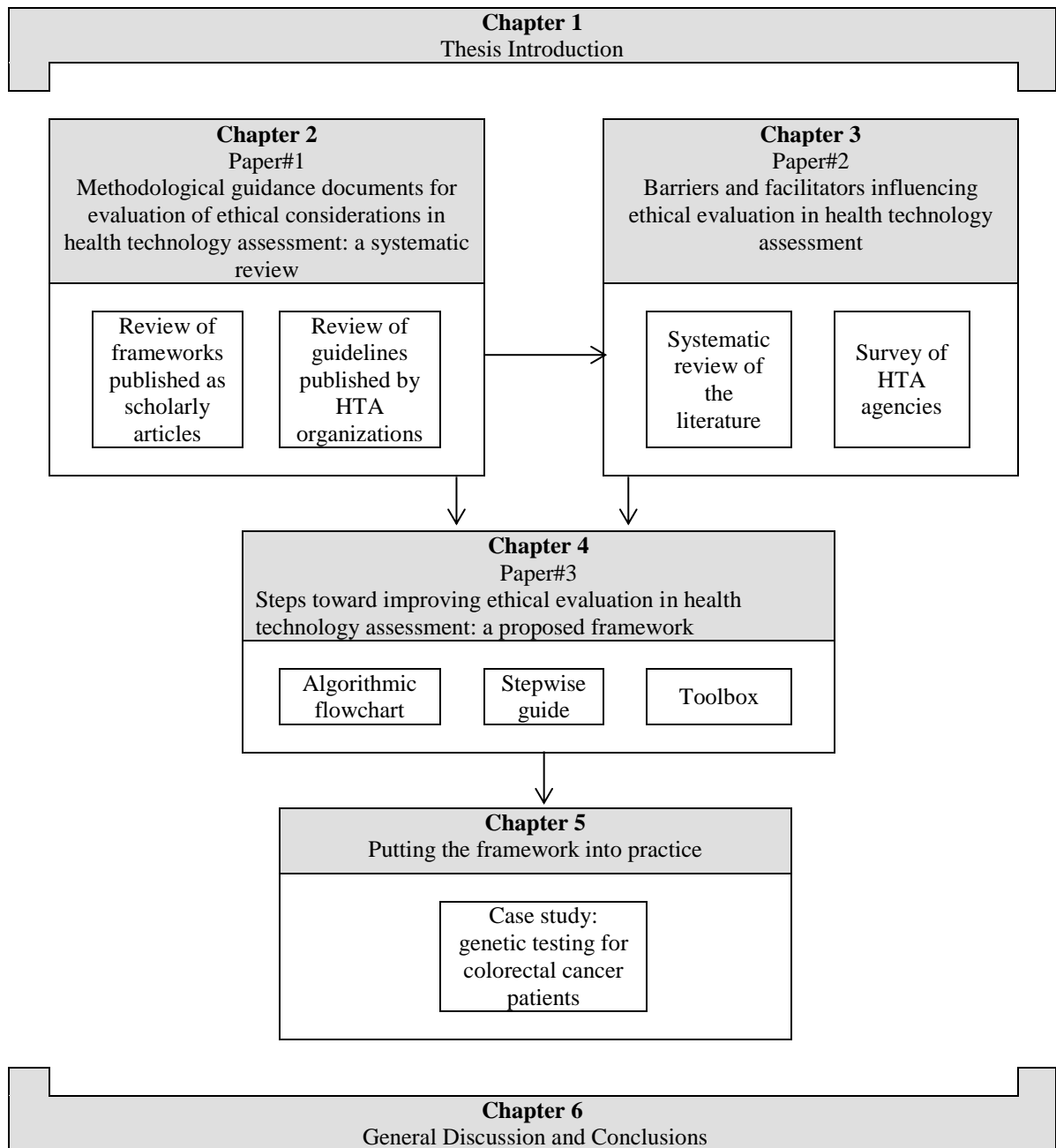Figure 1. Factors influencing incorporation of ethics in HTA

Figure 2. Overview of the thesis chapters

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CHAPTER 2

Methodological guidance documents for evaluation of ethical considerations in health technology assessment: a systematic review[1]

Short title: Methods for evaluation of ethics in HTA

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URL: http://www.tandfonline.com/doi/abs/10.1586/14737167.2014.894464

Summary:

Despite the advances made in the development of ethical frameworks for health technology assessment (HTA), there is no clear agreement on the scope and details of a practical approach to address ethical aspects in HTA. This systematic review aimed to identify existing guidance documents for incorporation of ethics in HTA to provide an overview of their methodological features. The review identified 43 conceptual frameworks or practical guidelines, varying in their philosophical approach, structure, and comprehensiveness. They were designed for different purposes throughout the HTA process, ranging from helping HTA-producers in identification, appraisal and analysis of ethical data to supporting decision-makers in making value-sensitive decisions. They frequently promoted using analytical methods that combined normative reflection with participatory approaches. The choice of a method for collection and analysis of ethical data seems to depend on the context in which technology is being assessed, the purpose of analysis, and availability of required resources.

Introduction

Health technology assessment (HTA) is defined as a multidisciplinary process of studying the medical, social, ethical and economic implications of development, diffusion and use of a particular health technology(1). Although there is a general consensus on the importance of ethical assessment as a part of HTA (2-4), the evaluation of ethical issues is frequently neglected in the development of the majority of HTA reports. An analysis of 680 HTA reports produced by six Canadian agencies between 1997 and 2006 shows that only 17% addressed ethical issues (5). A survey of 223 HTA reports, published between 2003 and 2006, by nine different agencies (five in Canada , two in the United Kingdom, one in Denmark, and one in the United States) showed that only 5% reports considered ethical, social and organizational issues, in addition to clinical and economic evaluations (6).

Given the different nature and goals of ethical evaluation, its scarcity in mainstream HTA is understandable (4). Unlike clinical and economic assessments, which seek to correctly explain and predict outcomes of a technology using empirical data, ethical analysis tends to look for ethical values and use philosophical theories to justify certain reasons for implementation of a technology or otherwise. Therefore, different approaches must be used to tackle ethical issues in HTA, in which HTA practitioners may not necessarily have specialized knowledge and skills. The current literature recognizes insufficient methodology as one of the challenges related to lack of incorporation of ethics in HTA

and highlights the need to improve methods of identifying and analyzing ethical concerns raised by healthcare technologies (2;3).

While advances have been made in the development of ethical frameworks for HTA, there is no clear agreement on the most useful and practical approach to address ethical aspects (7). Moreover, uncertainty remains about appropriate scope and level of details regarding ethical frameworks for HTA (8-11). A number of studies have been conducted to evaluate ethical analysis methods applied in HTA reports (8;9;11;12). These studies have described frequently used methodological approaches for addressing ethical issues, but none of them have critically evaluated characteristics of such methodologies.

The purpose of this article is to systematically review the literature to identify existing guidance documents for incorporation of ethics in HTA in order to provide a comprehensive overview of their methodologies and to gain a better understanding of the areas of commonality and divergence between different frameworks or guidelines.

Systematic review of the literature

Methods

Data sources and study selection

A systematic search of literature was undertaken, without limits of time and language, to identify methodological frameworks published up to 1 October 2013. The following bibliographic databases were searched through the Ovid interface: Medline, EMBASE,

and PsycINFO. Parallel searches were run in PubMed, Wiley's Cochrane Library, and the

Centre for Reviews and Dissemination's (CRD) HTA database. The search strategy

included a combination of text words and Medical Subject Headings terms and synonyms

of ethics, HTA, and methodology. Suggestions made by Droste (13) and Niederstadt (14)

were used as a guide for the selection of ethics-related search terms. The details of the

search strategy are presented in the Supplementary Material 1. Additionally, grey

literature was identified by searching the websites of selected HTA agencies

(Supplementary Material 1) and reviewing the bibliographies of key articles and through

contacts with appropriate experts.

Articles were included if they were methodological papers providing formal conceptual

or practical frameworks, models, or tools for dealing with ethical aspects of health

technologies; or HTA guidelines containing instructional guidance for addressing ethical

issues. Both generic and technology-sensitive guidance documents were deemed relevant

for inclusion. Citations that primarily offered a theoretical discussion or comments on if

and why ethics should be included in HTA were excluded from this review. Ethical

frameworks developed for assessment of non-healthcare technologies (e.g. information

technology) or for purposes other than HTA were also excluded.

Titles and abstracts of all articles were screened by two independent reviewers to exclude

the articles that clearly did not match the inclusion criteria. The remaining articles were

retrieved and assessed for eligibility by one reviewer and checked by a second.

Disagreements were resolved by consensus.

Data abstraction and synthesis

The included papers were grouped into: scholarly methodological articles presenting

ethical frameworks, models, or tools for HTA, from here on referred to as "frameworks";

and methodological guidance for incorporation of ethics in HTA, published by HTA-

related organizations, from here on referred to as "guidelines". Guidelines could be

published as manuals, handbooks, or online guidance documents. The articles were

thoroughly scrutinized to get a sense of common themes or methodological

considerations. All articles with a normative analysis component were read thoroughly to

identify the ethical theories they utilized as lenses to understand different issues around

health care technologies and as foundations to build their frameworks or models, such as:

utilitarianism (which promotes maximization of benefits for the greatest number of

people), deontological ethics (which focuses on duties, rules and obligations), virtue

ethics (which emphasizes moral character and virtues of individuals), or feminist

perspectives (which are concerned with context, power balance in decision-making, and

individual situations) (15). The guidance documents were further evaluated for their areas

of focus, and methodological approaches through which the users are instructed to

collect, appraise, synthetize, or interpret ethical data. Data were also abstracted on

practical tools provided to help address ethical issues, case studies presented to facilitate

understanding of the suggested approach or model in practice, level of stakeholder

engagement, and required expertise. The results were summarized in both text and tabular forms.

Results

A total of 1474 potential citations were identified through the systematic search, of which 1346 citations were excluded after title and abstract review, leaving 128 citations for the full-text assessment. Of these 128 citations, 85 were eliminated because they did not meet the eligibility criteria, leaving a total of 21 methodological articles and 22 HTA guidelines for inclusion in this review. Figure 1 shows the detailed study selection process.

Frameworks published as scholarly articles

All of the included frameworks were published in English, between 1999 and 2012. Seventeen of the 21 frameworks suggested a generic approach applicable to all health technologies (13;16-31), whereas the remaining four provided a methodological approach or model that could be used in the context of a specific group of technologies (32-35). A general summary of the included articles is shown in Table 1.

Theoretical foundation

None of the proposed frameworks or models was based on a single moral theory. The majority of authors either implicitly or explicitly pursued a pluralistic approach to explain

their conceptual or procedural frameworks. Moral pluralism, also referred to as an 'eclectic' approach by some authors (16;23;31), emphasizes examining a technology and its consequences from multiple ethical perspectives in order to arrive at a robust judgment, to address the complexity of ethical dilemmas and uncertainties around healthcare technologies, and to better justify HTA decisions (16-27;35).

Areas of focus

The authors of the included frameworks identified a wide range of ethical areas that might be relevant in HTA. Hofmann (23) listed a set of questions related to: fundamental moral issues, such as benefits and risks, autonomy, human rights, integrity, dignity, obligations, social and cultural values, legal issues and justice; stakeholders; technology; methodological choices in HTA; and the HTA process. The main ethical domains that were suggested by the remaining frameworks included: benefit and harm (safety) (13;18;28;32-34), autonomy (13;28;32-34), equity (fairness or distributive justice) (13;16;18;22;31), stakeholder values (21;22;25-29;31;35), utility (18), acceptability (20;31;34), psychological impact (20;31), impact on family and care-givers (31;33), quality of life (13;33), efficiency (18), opportunity cost (18;31), and ethical issues related to appropriateness of methods chosen for economic evaluations (17).

Procedural guidance

We classified the included frameworks to four general categories, based on the procedural approaches they took: reflection through ethical principles and theories

(classical methods), supplementing classical methods with participatory and interactive approaches, providing pragmatic tools for obtaining and synthesizing ethical data, and frameworks for discussion of ethical data for making HTA decisions.

Frameworks proposing classical methods for ethical reasoning

Principlism (28;32-34) justifies action through adherence to ethical principles. HTA, like most health related literature, generally promotes the use of Beauchamp and Childress' four fundamental principles of bioethics, including beneficence (responsibility to maximize benefits), non-maleficence (to avoid causing harm), respect for autonomy (respecting the decision-making capacity of individuals), and justice (equitable distribution of benefits and costs) (36).

Casuistry (24;29) is presented as a case-based reasoning method which starts from the description of a particular case and compares ethical dilemmas around this case with examples of ethical dilemmas related to similar cases to identify the paradigm that best fits the case.

Coherence analysis (26) attempts to reflect on the consistency of various ethical components that are generally used in ethical reasoning, such as theories, principles, and value judgments, without being directive in terms of which argument is more relevant.

Frameworks proposing classical methods supplemented by participatory approaches

Wide reflective equilibrium (WRE)(27) is described as a deliberative method for establishing a decisional balance through a broad social reflective process. In WRE stakeholders and citizens discuss the normative justification for a HTA decision until a state of balance is achieved within a wide set of moral values and beliefs.

Axiology-based value analysis (17;22) is a reasoning model that is concerned about values (beliefs and social attitudes as well as monetary values), their origins, inter-relationships and dynamics. Value analysis is presented as an approach for mapping values held by individuals or the society and studying their interactions or conflicts.

Triangular model (19) is a human-centered model for evaluation of healthcare technologies that recommends combining factual, anthropological and ethical data and synthesizing through a normative reflection process.

Based on this conceptual framework of the complexity theory (21), a large number of inter-related technological and environmental factors should be taken into account in the evaluation of healthcare technologies. The framework seeks to involve stakeholders in the assessment and take into account the uncertainty due to complex and unpredictable interactions between technology and its environment, including ethical and social dimensions.

Similar to the complexity framework, actor-network theory (35) approach recognizes the need for consideration of a complex network of scientific, technical, social and political actors in HTA, and describes potential inter-relationships between actors, interactions with the environment, and technological change due to time- and context-dependent changes in attitudes and behaviours of the actors toward the technology.

The social shaping of technology framework (20;25;26) emphasizes co-shaping of technology and society and promotes deliberation on social and ethical issues around technology earlier on in the technology development process when such considerations can influence the design and use of the technology.

Frameworks providing pragmatic tools for obtaining and synthesizing ethical data
Droste *et al* proposed a framework for the identification and retrieval of ethical data for HTA. They recognized the need for a systematic search of ethical information using a procedure similar to the one used for the assessment of clinical benefits (13). The authors suggested specific search terms, databases and examples of ethics-related search strategies, however, emphasized that other data sources such as expert advice might also be needed.

Some frameworks provided practical tools for HTA-procedures to evaluate and report ethical aspects of healthcare technologies in a structured manner. These tools mainly included eclectic checklists consisting of generic or context-sensitive ethical questions as

road maps for ethical reflection (16;23;33). The authors of these articles believed that no

single ethical theory can cover all of ethical concerns around a health technology. They

suggested that evaluation of ethical issues in HTA should include a variety of questions

reflecting different perspectives and normative theories, and the information related to all

of the relevant questions should be synthesized in the process of ethical reasoning. For

example, Hofmann (23) presented a series of 33 ethical questions related to the

development and use of healthcare technologies. Mahoney *et al*. (33) recommended the

question-based checklist of ethical principles and guidelines for gerontechnology

research and development, as a model framework for the analysis of ethical

considerations related to home monitoring. The equity framework proposed by Culyer *et

al.* (16) provided a comprehensive checklist of questions that could be used in various

phases of a HTA process from selection of a candidate technology to discussion of equity

considerations by advisory committees during the assessment and decision-making

phases.

*Frameworks and models proposed for combining ethical evidence with other types of

evidence in HTA*

Two Canadian frameworks introduced multi-criteria methodologies that explicitly

included ethical considerations as an element that decision-makers should consider when

choosing between healthcare technologies (18;30). Johnson *et al.* recommended four

determinant criteria to be included in HTA decision-making processes: clinical benefit,

consistency with ethical and social values, cost-effectiveness and feasibility of

implementation (30). They required the evidence on the proposed criteria be obtained

through a systematic literature review and discussed in a deliberative public engagement

process before HTA professionals and decision-makers could make their

recommendations on the new health technologies. A decision support tool using the

multicriteria decision analysis framework was provided by Goetghebeur *et al.* (18) to

facilitate a structured decision-making process based on HTA. The tool focused on

quality of evidence, disease severity, and efficacy of interventions, cost-effectiveness, as

well as ethical principles of utility, efficiency and fairness. The authors exemplified their

proposed framework with the help of a case study, where they demonstrated how the

information from the literature and stakeholder opinions can be converted to an

multicriteria decision analysis matrix and how the information in the matrix should be

processed and scored with the help of experts in order to rank the alternative healthcare

technologies.

Stakeholder engagement

Fourteen frameworks emphasized on the need for assessment of ethical aspects through

stakeholder involvement or a broader social discourse (17;19-23;25-31;35). The proposed

participatory models were categorized thematically, based on the level of stakeholder

engagement, to the following types: consultative models (17;19;21-23;30;31;35) in which

a range of relevant stakeholders are contacted in order to learn about their personal and

societal values and to obtain their concerns about the technology, alternatives and the

impact of potential decisions; interactive models (26-29) that involve experts,

stakeholders and citizens in a deliberative process in order to identify, discuss and reflect on the ethical aspects of a technology; and constructive models (20;25) that emphasize a mutual influence of technology and society, and argue that in order to have an impact on the design of the technology, public engagement should take place early in the development process. Consultative methods seek information from stakeholders as inputs for ethical analysis or a decision-making process, whereas interactive or constructive models are more participative and are based on argumentation, public reasoning and agreement.

The included frameworks suggested a number of participatory techniques in order to collect primary data on stakeholders' values and behaviours. These included: awareness initiatives (20), social controlled experiments (20;25), circle of conversations (26;28;29), focus group discussions (28), dialogue workshops (20), Delphi technique and consensus conferences (20;25;26). Some frameworks stressed the integration of quantitative and qualitative data for the purpose of ethical analysis (21;24;28).

Need for ethical expertise
Although the necessity of ethical knowledge was implied in all of the included frameworks, six of the included frameworks highlighted the role of ethical expertise in providing inputs for preparing the search strategy (13), making normative judgments (26;31), and providing ethical knowledge required for deliberative ethical analysis or decision-making processes (16;22;26).

Guidelines published by HTA organizations

Twenty-two guidelines were included in this review. Six of the guidelines were developed by international/multi-national organizations such as the World Health Organization (WHO) (37), the European Network for Health Technology Assessment (EUnetHTA) (38), the International Network of Agencies for Health Technology Assessment (INAHTA) (39;40), or the European Union (41;42); while the remaining 16 guidelines originated in European countries (n=14), particularly Austria (43), Belgium (44), Denmark (45), Germany (46;47), Ireland (48), Norway (49), Poland (50), Spain (51), Sweden (52), Switzerland (53), and the United Kingdom (54-56); followed by Canada (n=2) (56;57), and Thailand (n=1) (58). More than half of the guidelines were published in or after 2006 (n = 15) (38;39;43-46;48-56). Documents' publication language was either English (n=16) (37-42;44;45;48;50;53-58), German (n=3) (43;46;47), Spanish (n=1) (51), Swedish (n=1) (52), or Norwegian (49). Two guidelines intended to offer guidance for preparation of HTA reports (39;57), 15 provided a generic procedural framework for HTA with ethical analysis included as a part of the HTA methodology (37;38;41-46;48;50;52;53;55;56;58), and five explicitly focused on methodology for addressing ethical issues in HTA (40;47;49;51;54). The guidelines differed in terms of their comprehensiveness and practicality. Two guidelines emphasized on inclusion of ethical issues in HTA with little instructions to follow (39;46), but the remaining guidelines provided instructions at various levels of details for the collection,

analysis and reporting ethical data. A general summary of the included guidelines is shown in Table 2.

The HTA Core Model, developed by EUnetHTA (38), provided structured guidance for developing HTA reports, along with frameworks for application of the Core Model for the assessments of medical and surgical (59), diagnostic (60), and screening technologies (61), as well as rapid relative effectiveness assessment of pharmaceuticals (62). The model included nine domains: health problem and current use, description and technical characteristics, safety, effectiveness, costs and economic evaluation, ethical, organizational, social, and legal aspects. Each domain consisted of a number of topics, and each topic covered several issues. The ethical domain of the Core Model included a checklist of questions covering ethical issues related to the technology and the HTA process, along with a brief description of commonly used methods to answer the questions, and the ways through which ethical evaluations should be integrated into HTA (Table 2).

Guidelines developed by the European HTA agencies who participated in the development of the HTA Core Model seemed to follow a similar methodological approach with some between-country variations. Country-specific guidelines published by the Swedish (52), Norwegian (49), Spanish (51), Danish (45), Austrian (43), and German (47) agencies suggested similar systematic approaches to guide ethical evaluation providing sets of steps associated with preanalysis planning, identification of

ethical issues, stakeholder involvement, ethical analysis and summarizing the ethical

information. Similar to EUnetHTA's Core Model, these guidelines allowed using

different procedural approaches for ethical analysis. Four of the guidelines suggested

using checklists with questions drawn from Hofmann's question list (23) to help identify

ethical issues (38;40;49;51).

The majority of the above-mentioned guidelines described available methodologies for

ethical analysis. However, some expressed no preference for the choice of method, while

others focused their instructions on a specific approach. For example, Swedish guidelines

promoted the use an "actor model" that considers ethical concerns related to various

structural and individual actors based on basic ethical principles (52). Three of the

guidelines introduced an 'ethical matrix' as a tool for analyzing ethical issues related to

different stakeholders based on ethical principles (52), stakeholders' values and

perspectives (43), or consequences of implementation of the technology or otherwise

(51).

As can be seen in Table 2, the included guidelines also varied in specifying the types of

ethical issues that should be incorporated in HTA. Some focused on integration of ethical

and economic analyses by balancing cost-effectiveness against equity (48;50;54-58),

while others encouraged consideration of basic ethical principles (45;47;52;54;63),

patient rights (44;45;53), or stakeholder values (40-44;49-51).

The National Institute for Health and Clinical Excellence (NICE)'s social value judgments (SVJs) document recommended that a combination of scientific and social values of heath technologies should be taken into account in the health technology appraisal process (54). The document provided a description of the principles that should be considered in making SVJs, and guidance on how SVJs should be used by NICE's advisory bodies to make HTA decisions. However, NICE did not recommend weighting cost-effectiveness estimates based on social values (55). Similarly, the guidelines developed by the national HTA agencies in Canada (56;57), Ireland (48), Poland (50), and Thailand (58), which included recommendations regarding incorporation of equity issues and social preferences in economic evaluations, did not allow equity weights to be applied to the results of cost-effectiveness analyses (table 2).

Expert Commentary

Our systematic review identified multiple guidance documents for incorporation of ethical considerations in HTA, varying in their philosophical approach, structure, and comprehensiveness. We also found that ethical guidance documents have been designed for different purposes throughout the HTA process. These purposes range from helping HTA producers in identification, appraisal and analysis of ethical data to supporting decision-makers in making better informed, value-sensitive decisions.

Some of the identified frameworks were designed for use in a particular context, while others were generic. Although the included frameworks seemed to have originated from

slightly different lines of thinking, the majority of them supported utilization of multiple

ethical principles and theories to address ethical issues from different perspectives. They

frequently promoted combining normative reflection with descriptive approaches to the

analysis of values and preferences of potential stakeholders and other societal or technical

actors. The nature of the proposed procedural approaches differed widely. They varied

from the approaches that basically gave a general way of thinking about how to approach

the assessment of ethical issues in HTA to those that provided analytical tools or case

studies to aid the users' understanding of a particular ethical analysis method. However,

there were limited guidelines provided on how to perform such analyses.

Our findings are similar to those of Saarni *et al.* who reported the results of a survey on

methodologies used by HTA organizations for the assessment of ethical considerations

(11). They listed casuistry, coherence analysis, principlism, participatory HTA

approaches, social shaping of technology and WRE as the commonly used methods by

HTA producers up to the time of publication of their paper in 2008. Further approaches

used by individual European HTA organizations were also referenced in this article, such

as value analysis, triangular model, and eclectic or context-specific integrated

approaches. Potter *et al.*, who performed a review of HTA and policy evaluation

frameworks in the field of genetic screening and public health genomics, identified three

general approaches recommended for integration of ethical, social and legal aspects in

HTA, including: synthesis of literature, expert advice, and consideration of stakeholder

values (12). The reviewed frameworks included a number of ethical issues related to

genetic testing such as human rights, equity, autonomy, stigmatization and

discrimination, psychological consequences, acceptability, confidentiality, and

intellectual property. The authors recognized the lack of methodological guidance for

evaluation of ethical and social consideration as an important challenge for HTA

producers. Similarly, through content analysis of published HTA reports, Lehoux and

Williams-Jones identified three main mechanisms for evaluation of ethical issues in HTA

reports: expert advice, primary or secondary research, and participatory approaches (8).

They found theoretical approaches that were relevant to bioethics and social sciences

prevalent in evaluation of ethical issues in HTA reports.

Our review differs from the above studies in several aspects. First, we used a systematic

approach to identify formal frameworks for ethical considerations in HTA. Second, the

potential sources for data were broader and no limitations of language and year of

publication were applied. Third, our review provides a structured summary of the ethical

frameworks and guidelines for a better understanding of different methodologies.

Choosing between frameworks

Our review found no common approach that could be used for ethical analysis in HTA.

Additionally, we found limited guidance on specific circumstances in which each

analytical approach could be appropriate. Thus, it seems difficult to choose a procedural

approach that allows for optimum integration of ethical issues in HTA. When deciding

which framework to use, it is important to consider the appropriateness of the framework

for a given context, the objective of ethical analysis, and the way in which the framework

addresses problems within its target application domain (e.g. genetic technologies).

Prior to the utilization of a framework, it is also important to consider its potential

weaknesses and limitations. In general, normative approaches require an adequate

knowledge of ethics and ethical theories, which may not be available within most of HTA

organizations. In addition, most of the analytical methods in this category are prone to

subjective bias, i.e. the assessment may vary between different assessors or contexts (28).

Theoretical frameworks may also have some limitations with respect to the validity and

generalizability of their results. For example, in using ethical principles there might be a

conflict between two or more of the principles. A classic type of conflict is between the

principles of respect for autonomy and beneficence (36). Since the principlist approach

does not weight the principles, researches might need to prioritize the conflicting

principles, a judgment which is often decided by intuition alone, although evaluation,

debate and consensus are much sounder and more generalizable (in Canada, for example,

principles could be derived from consensus about the values in the Canada Health Act).

Casuistry is another commonly used normative method that suffers the potential

limitations of relying on subjective analogic arguments and intuitive judgment about a

particular case (24). On the other hand, the descriptive approaches (value research) that

frequently employ public involvement methods also appear to have a number of

limitations. They might be costly, time consuming and complex to perform. Other

possible challenges to consider are willingness of stakeholders to participate,

representativeness of participating public groups, complexity of the collection and processing of qualitative data, the institutional barriers related to the attitudes of researchers and the availability of competent expertise (64).

Currently available evidence on how different methods might be effectively used for ethical evaluation in HTA is limited. Saarni *et al.* compared the results of four analytical methods (axiology, casuistry, principlism and EUnetHTA Core Model) in evaluation of ethical issues related to bariatric surgery (10). The authors who obtained similar results with all four methods concluded that the results produced by a given ethical analysis approach could be 'transferable between methods'. Further research is needed to compare different frameworks when they are applied to different types of technologies or to different contexts.

Diversity of guidelines

One of the notable findings of this review was the diversity in the scope and depth of ethical assessment methods recommended by different HTA agencies. Some agencies recommended a systematic approach to guide different steps of an ethical evaluation from identification of ethical issues to analysis and reporting; while others concentrated their recommendations on addressing societal values or equity issues in HTA. This variation seems to reflect differences in health care systems in which the HTA agencies operate and degree of the agencies' connection to decision-making (65). Further research is required to better understand how institutional aspects of HTA organizations and their

relation to policy decisions can influence their approach to the assessment of ethical considerations.

Role of experts

Although not explicitly recommended, in all of the reviewed frameworks ethical expertise was deemed implicitly necessary for conducting an ethical analysis.

In the literature, it has been argued that the role of ethicists is important in the incorporation of ethical considerations in HTA (8;9;11;26). However, in discussion surrounding the expert role, a distinction should be made between the top-down and bottom-up approaches for ethical analysis. In classical methods (e.g. principlism, casuistry, or coherence analysis) the normative assessment of ethical aspects is generally performed with the help of experts with knowledge of ethics in a top-down manner. On the contrary, in participatory approaches, stakeholders and citizens are involved in a bottom-up process of technology appraisal and decision making. In conducting participatory assessments, HTA practitioners and ethicists can play an active role in public and political debates by providing scientific and theoretical inputs and assisting stakeholders in reaching a consensus (26). They also might act in an advisory capacity to justify and provide rationale for different approaches for ethical analysis (26). Further research is needed to determine the relative weight that should be given to expert and democratic inputs in the assessment of ethical aspects of healthcare technologies.

Five-year view

Our systematic review identified a range of approaches to aid consideration of ethical issues throughout the HTA process; yet, no generally accepted way was found. The choice of a method for collection and analysis of ethical data seems to depend on the context in which technology is being assessed, the purpose of analysis, and availability of required resources.

The identified methodologies predominantly use participatory methods as complementary methods to classical approaches of normative ethical analysis. It is evident that the formal HTA has been undergoing a shift from being a largely science-oriented expert-driven tool for guiding policy decisions to being a method for the assessment of scientific, technological and wider ethical and social aspects of healthcare technologies through a social communicative process between HTA professionals, technical experts and stakeholders. However, in some jurisdictions, this transition may need organizational and social transformations to occur.

It is important to note that the scope of this systematic review was limited to identification and description of existing frameworks for ethical assessment in HTA, rather than comparing methodological features of different frameworks. We suggest that future research should not only focus on comparison of alternative methods of addressing ethical issues in HTA, but also assess their practicality, applicability to various contexts, and impact of their results on decision-making processes. In addition, we focused our

review on frameworks and guidelines developed specifically for ethical analysis in HTA. Other ethical frameworks might exist that have primarily been developed for the assessment of nonhealth technologies, but might also be useful in HTA. Future researchers are encouraged to extend this work to include literature from other technology areas.

Key Issues

- The current guidance documents for ethical considerations in HTA are designed for different purposes throughout the HTA process such as helping HTA producers in identification, appraisal and analysis of ethical data, and supporting decision-makers in making better informed value-sensitive decisions.
- The existing guidelines seem to vary in terms of their focus and recommendations across different HTA agencies, based on the type of organization and its decision-making process.
- Four general procedural approaches are proposed for ethical analysis in HTA: reflection through ethical principles and theories, supplementing classical methods with participatory approaches, providing pragmatic tools for obtaining and synthesis of ethical data, and integrating ethics in multicriteria HTA decision-making tools.
- Ethical frameworks frequently use analytical methods that combine normative reflection with participatory approaches, where stakeholders and citizens share and discuss different viewpoints and arguments.

- Existing methods are generally meant to be used by professional ethicists or HTA practitioners with a knowledge and skill in ethical analysis.

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Figure 1- Study selection flow diagram


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┌─────────────────────────────┐   ┌─────────────────────────────┐
│ Records identified through  │   │ Additional records identified│
│ database search (n= 1931)   │   │ through other sources (n=31)│
└─────────────────────────────┘   └─────────────────────────────┘
              │                                 │
              ▼                                 ▼
        ┌───────────────────────────────────────┐
        │ Records after duplicates removed      │
        │ (n= 1474)                             │
        └───────────────────────────────────────┘
                          │
                          ▼
        ┌───────────────────────┐        ┌─────────────────────┐
        │ Titles and abstracts  │───────▶│ Records excluded    │
        │ screened              │        │ (n = 1346)          │
        │ (n = 1474)            │        └─────────────────────┘
        └───────────────────────┘
                          │
                          ▼
        ┌───────────────────────┐        ┌──────────────────────────────┐
        │ Full-text articles    │        │ Full-text articles excluded, │
        │ assessed              │───────▶│ (n = 85)                     │
        │ for eligibility       │        │                              │
        │ (n = 128)            │        │ Reasons for exclusion:       │
        └───────────────────────┘        │ − Academic discussion papers │
                          │              │   on ethics and HTA (39)     │
                          ▼              │ − HTA-related frameworks or  │
        ┌───────────────────────┐        │   guidelines with no ethics  │
        │ Articles included     │        │   component (24)             │
        │ (n=43)               │        │ − Ethical frameworks not     │
        │                      │        │   related to HTA (7)         │
        │ Scholarly articles   │        │ − Systematic or qualitative  │
        │ (21)                 │        │   reviews (9)                │
        │                      │        │ − Duplicate publications (4) │
        │ HTA guidelines (22)  │        │ − unable to translate (2)    │
        └───────────────────────┘        └──────────────────────────────┘
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Table 1- Overview of the included methodological scholarly articles to address ethical issues in HTA

First author, Year	Country of origin	Methodological Approach	Description	Ethical Analysis Tools	Case Study	Ref.
Culyer and Bombard (2012)	Canada	An eclectic approach for consideration of equity issues	This framework for HTA lists 13 equity domains to be taken considered in HTA procedures and decisions. These include: "equity vs. equality, adequacy of domains of equity, legal obligations, general principles, embedded inequity, institutional bias, implicit stereotyping, contexts and circumstances, processes in HTA, hidden opportunity costs, processes in delivery of care, special claims, and cumulative effects".	A checklist consisting of sets of questions for various domains of framework	None	(16)
Burls *et al*. (2011)	Multinational	Ethical reflection at the axiological level	This context-sensitive framework, which consists of targeted questions about the characteristics of a selected technology and ethical issues around its implementation and use, has been developed based on the recommendations of a group of experts from 16 INAHTA member agencies.	A set of 13 questions	None	(17)
Goetghebeur *et al*. (2010)	Canada	Multi-criteria decision analysis (MCDA)	The framework includes 4 quantifiable (quality of evidence, disease, intervention and economics) and 6 non-quantifiable (3 ethical and 3 healthcare system related) elements to facilitate decision-making about health technologies. The ethical component suggests the principles of utility, efficiency and fairness to be considered in combination with the goal of healthcare, opportunity costs and population priorities.	MCDA value matrix consisting of questions related to 15 quantitative and 6 ethical and system-related components.	Growth hormone for turner syndrome	(18)
Droste *et al*. (2010)	Germany	Systematic retrieval of information	The article recognizes the need for a separately performed systematic search of information related to ethical aspects of health technologies and proposes a multi-step methodology for identification and selection of available information sources, designing and execution of	Search terms and strategies tailored to relevant information	None	(13)

First author, Year	Country of origin	Methodological Approach	Description	Ethical Analysis Tools	Case Study	Ref.
			search strategies, retrieval of information, reporting the search results, and relevant quality check practices.	sources		
Sacchini *et al.* (2009)	Italy	Triangular model for integrating ethics in HTA	This model seeks to relate biomedical, anthropological and ethical aspects of health technologies through three steps: collection of factual data about the technology; anthropological analysis to understand values and justify facts; and ethical evaluation at a normative level to guide decision-making.	None	None	(19)
Johnson *et al.* (2009)	Canada	A multi-criteria framework for HTA decisions	The framework suggests the following decision determinan be considered in HTA: clinical benefit, consistency with societal and ethical values (related to the technology and its consequences), value for money, and feasibility of adoption into the health system, as decision determinants that should be considered in HTA.	None	None	(30)
Autti-Ramo and Makela (2007)	Finland	eclectic approach	The article suggests an eclectic approach for evaluation of ethical aspects related to the technology and consequences of its implementation be evaluated continuously throughout the HTA process (with the help of an ethical expert, if needed). The authors' emphasis on identification of related stakeholders and repeating the ethical appraisal a few times during the HTA process. Ethical considerations are recommended to be presented in a separate chapter.	None	None	(31)
Douma *et al.* (2007)	Netherlands	Constructive technology assessment	The method focuses on dynamics of technology and its interactions with the environment/society; and suggests that, depending on dynamics of development and implementation of technology, the assessment should address a combination of clinical, economic, and patient-	None	Microarray analysis for breast cancer	(20)

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First author, Year	Country of origin	Methodological Approach	Description	Ethical Analysis Tools	Case Study	Ref.
			related (social/ environmental impact, ethics, acceptability, psychological reactions, patient-centeredness, etc.) and organizational aspects.			
Lessard (2007)	Canada	Complex adaptive systems (complexity) theory	This conceptual framework recognizes the complexity of assessment of healthcare technologies and the importance of reflexivity and consideration of contextual elements (individual and societal) and multiple perspectives in economic evaluations of health technologies.	None	None	(21)
Hofmann (2005)	Norway	Value analysis/ axiology	The article presents a conceptual framework for thinking about value-ladenness of technology and various aspects of HTA (e.g. scientific, economic, , professional and moral) and emphasizes on the importance of identifying values involved in development, implementation and utilization of the technology and discussing the interrelation between different types of values.	None	None	(22)
Hofmann (2005)	Norway	Moral pluralism	The article seeks to introduce a practical eclectic approach to address moral issues in HTA and provides a list of questions concerning a wide range of moral issues related to the technology, the stakeholders and the HTA methodology and process. Various questions in this checklist present different moral theories, e.g. utilitarian, deontological, principlism, social shaping of technology, casuistry, virtue ethics and critical theory.	A checklist of 33 moral questions	None	(23)

First author, Year	Country of origin	Methodological Approach	Description	Ethical Analysis Tools	Case Study	Ref.
Giacomini (2005)	Canada	Casuistry	Casuistic analysis (case-base decision making by analogical reasoning) is suggested to be performed through appraisal of the technology and resources required for its implementation, through identification of precedent technologies (paradigmatic cases) similar to the technology of interest, comparison by analogy and integrating the results to the decision-making cycle.	None	IVF, Viagra, and predictive genetic testing	(24)
Clausen and Yoshinaka (2004)	Denmark	Social shaping of technology	This analytical approach is concerned with the mutual influence of technology and society on shaping of technology. The method regards technological (content) and societal (context) aspects of the technology equally important and suggests that ethical analysis should address the roles and values of different actors and their interactions in the course of development and assessment of technology, through interactive methods such as consensus conferences.	None	Laparoscopic cholecystectomy	(25)
Grunwald (2004)	Germany	Social shaping of technology and Coherence analysis	This analytical approach realizes that ethical arguments should be justified by their coherence with diverse ethical theories and principles, and the moral beliefs held in society, without justifying the beliefs as right or wrong. The following areas are encouraged to be addressed: (a) society's current normative framework; (b) society's expectations of the technology and its impact; (c) objectives and visions of society; and (d) analysis of society's present nature and capacity	None	None	(26)
Reuzel et al. (2001)	Netherlands	Wide reflective equilibrium through	The framework requires a "newly established" and "inter-subjective" agreement achieved through participation of various stakeholders in an interactive assessment of the technology. This is a process by which stakeholders and	None	None	(27)

First author, Year	Country of origin	Methodological Approach	Description	Ethical Analysis Tools	Case Study	Ref.
		interactive technology assessment	citizens arrive at a wide and full reflective equilibrium, after examining their values through an extensive deliberation.			
Van Der Wilt *et al.* (2000)	Netherlands	Interactive technology assessment	The framework proposes a "circle of conversations" with all potential stakeholders to evaluate their perspectives (concerns, norms and values) through interviews and other interactive research methods such as Delphi technique.	None	Cochlear pediatric implants	(28)
Reuzel *et al.* (1999)	Netherlands	Casuistry imbedded in interactive technology assessment	This framework proposes a "circle of interviews" to evaluate stakeholders perspectives about the technology. Casuistry (analysis of moral issues by analogy) is suggested to be used during this interactive evaluation to compare different cases and clarify ethical concerns.	None	Cochlear pediatric implants	(29)
Technology-specific frameworks or models					**Technology Focus**	
Kidholm *et al.* (2012)	Multinational	Ethical principles (human dignity, access, equity)	This structural model for applications of telemedicine has been developed based on domains and elements of the HTA Core model(38) classifies sociocultural, ethical and legal aspects in one category, and requires consideration of all ethical questions raised by the technology and the consequences of its implementation in the assessment.	None	Telemedicine	(32)
Mahoney *et al.* (2007)	USA	Ethical reasoning based on evidence and moral principles	The model positions humanistic issues (e.g. disability, autonomy, quality of life, respect for family caregivers and family relationships) in the center as "core priority" concerns. Research needs and societal issues around the technology form the outer layers of the model.	A list of ethical principles and guidelines for gerontechnology research	Tele-health for persons with dementia	(33)

First author, Year	Country of origin	Methodological Approach	Description	Ethical Analysis Tools	Case Study	Ref.
Elsner (2006)	Australia	Ethical principles	The model identifies possible risk categories related to children born through reproductive cloning or other assisted reproductive technologies and determines whether it is acceptable to use such technologies by balancing reproductive freedom and safety concerns (autonomy versus non-maleficence).	None	Assisted reproductive technologies	(34)
Williams-Jones and Graham (2003)	UK	Actor-network theory	This analytical approach considers the potential moral, social and economic dilemmas of various stake-holders in HTA through the following concepts: actor-networks: human and non-human actors (institutions, groups and technologies); translation: the process of negotiation of common interests between human and non-human actors; and drift: the transformation of a technology as a result of its use in new social and technological contexts.	None	Commercial genetic testing (BRACA)	(35)

BRACA genes= tumor suppressor genes, also known as the breast cancer genes; CHD= coronary heart disease; CP= cerebral palsy; IVF= in vitro fertilization; UK=the United Kingdom; USA= the United States of America

Table 2- Summary of guidelines of HTA organizations for inclusion of ethical issues in HTA

Country/ organization Publication type	Year	Description	Tools/instruments	Ref.
International/ WHO				
Equity-based HTA toolkit [online]	2004	The toolkit integrates equity-oriented components (e.g. gender equity, social justice and community participation) a four step need-based HTA-toolkit that focuses burden of illness, community effectiveness, economic evaluation and knowledge translation and implementation.	Web links to commonly used tools for each of the suggested four steps	(37)
International/ INAHTA				
Checklist for HTA reports	2007	The checklist categorizes ethical, social, legal, economic, and organizational issues under a context-specific question that may not be addressed in all HTA reports. The box related to ethical aspects should be checked if ethical issues including access, equity and informed consent have been considered and the related methodology for ethical analysis has been described.	None	(39)
Report of working group on handling ethical issues	2005	The guidance document suggests a context-sensitive integration of a wide range of ethical consideration related to the technology itself and its consequences based on basic moral principles, society's underlying values and stakeholders' values and preferences. This should be performed as an ongoing process in all phases of HTA.	Hofmann's 33 questions	(40)
Multinational/ EUnetHTA				
HTA core model	2008	The ethical domain of the Core Model includes 18 questions covering 8 topics: principal questions, autonomy, human dignity, beneficence/non-maleficence, justice and equity, rights, legislation, and effectiveness/accuracy. The model also provides a brief explanation of methods that have been commonly used to answer these types of questions, and a discussion about integrating ethical reflection in all phases of the HTA process.	Table of ethical assessment elements Matrix of stakeholder-ethical consequences	(38)

Country/ organization Publication type	Year	Description	Tools/instruments	Ref.
Multinational/ EU				
ECHTA's HTA practice guidelines	2002	This framework suggests a systematic review of available literature (including qualitative research) and ethics expert consultation as the primary approaches for collection and appraisal of data on psychological, social and ethical issues. In case of lack of evidence, primary data collection is recommended through individual interviews, focus group discussions, Delphi technique, consensus workshops or patient satisfaction/acceptance survey questionnaires.	None	(41)
EUR-ASSESS' methodological guidance for HTA	1997	The guidance document encourages interactive technology assessment through the following steps: Identification of all stakeholders (potential agents, beneficiaries, and victims) and inquiring about their expectations and concerns, constructing an analytical model to include the above information, re-checking the model with the stakeholders and reaching to an agreement through negotiations Documentation of the above process, the expectations and concerns and suggestions for future activities, should be a part of the HTA report.	None	(42)
Austria/ GmbH				
HTA handbook	2011	The guidelines group psychosocial, ethical, legal and organizational aspects under socio-cultural considerations and suggest a perspective-oriented analysis based on a two-dimensional matrix with stakeholders along one axis and socio-cultural aspects along the other axis.	Socio-cultural matrix	(43)

Country/ organization Publication type	Year	Description	Tools/instruments	Ref.
Belgium/KCE				
HTA Process Notes	2007	The guidelines emphasize on the collection and appraisal of ethical evidence at patient and societal levels. Various methodological approaches are proposed for the search of ethical and social information around the technology.	None	(44)
Canada/CADTH				
Guidelines for economic evaluations of health technologies	2006	The guidelines suggest that equity considerations should be taken into account by making implicit and explicit equity assumptions, identifying equity-related subgroups of technology beneficiaries, and analysis of the distributional impact of the technology across the equity-related subgroups. Incorporation of equity weights in the base-case analysis in not recommended.	Matrix of equity-related subgroups and distributional or cost-effectiveness impact	(56)
Guidelines for authors of HTA reports	2001	The guidance document groups ethical, equity and psychological issues in one category and encourages HTA-producers to balance efficiency (cost-effectiveness) against equity. The consideration of procedural issues (preferences and choices, confidentiality) and psychological factors (patient satisfaction, acceptance, family concerns) is also suggested.		(57)
Denmark/ DACEHTA				
Danish HTA model	2007	The main elements of this HTA model are listed as technology, organization, patient, and economy. Ethics have been included under the element of "the patient". Exploration of the patient aspects of a health technology, including ethical considerations, ethical choices and ethical dilemmas is recommended. Ethical analysis is suggested to include all aspects of HTA, not just the patient aspect, based on the four basic ethical principles.	None	(45)

Country/ organization Publication type	Year	Description	Tools/instruments	Ref.
Germany/ DAHTA-DIMDI				
HTA handbook	2008	The document recognizes necessity of addressing ethical, social and legal aspects in HTA without providing a detailed methodological guidance. The above aspects are encouraged to be addressed in the Discussion section, if they cannot be addressed during the HTA process.	None	(46)
Methodological guidance for ethics in mini-HTA reports	2003	The guidance document suggests an extensive literature review to identify ethical issues, a qualitative analysis to examine and categorize ethical issues to medical, psychological, social, etc., followed by an ethical analysis in each category based on basic ethical principles and further context-specific criteria, if needed.	None	(13)
Ireland/ HIQA				
HTA guidelines	2010	The guidelines suggest that equity considerations should be included in HTA reports through addressing "unmet needs" of disadvantaged populations. However, equity weights should not be incorporated in economic analysis .	None	(48)
Norway/ NOKC				
Methodological guidance for ethics in HTA	2008	The document suggests a 6-step procedure to address moral issues in HTA, consisting of identification of moral challenges, identification of stakeholders, selection of relevant moral questions, literature search, analysis of moral questions based on literature search, stakeholder hearings, and summarizing the process. A list of 32 moral questions (related to health technology, stakeholders, methodological choices and HTA itself) is provided to guide the ethical analysis. Different approaches for ethical analysis are described and the basic steps for each method are provided.	A checklist consisting of 32 ethical questions	(49)

Country/ organization Publication type	Year	Description	Tools/instruments	Ref.
Poland/ AHTAPol				
HTA guidelines	2009	The guidelines encourage the assessment of impact of implementation of the technology on various stakeholders, equality and equity issues, patient satisfaction, social acceptance and psychological consequences of the technology. The identified ethical and social issues are suggested to be included in a SWOT† analysis along with economic aspects.	None	(50)
Spain/ UETS				
Methodological guidance for ethics in HTA	2010	The guidance document provides a methodological tool (checklist) to guide the ethical analysis, through adaptation and modification of the EUnetHTA's Core Model(38) and Hofmann's suggested moral questions(23). Different approaches for ethical analysis are described and the basic steps for each method are provided.	A checklist consisting of 31 ethical questions + 5 questions specific to diagnostic technologies. Stakeholder-ethical consequences matrix Search strategy (proposed by Droste)(13) for structured ethics-related lit search	(51)
Sweden/ SBU				
HTA handbook	2013	The document emphasizes on the use of basic ethical principles in all phases of HTA with a focus on patient perspective, stakeholder engagement and identification of ethical issues around the current practice (effectiveness, safety and cost-effectiveness versus equity). A matrix of valuation of technology consequences for different stakeholders is suggested for conduction of ethical analysis.	Matrix of stakeholder-ethical consequences	(52)

Country/ organization Publication type	Year	Description	Tools/instruments	Ref.
Switzerland/ INNOVAL				
HTA consensus document	2012	The document describes HTA as a normative process focused on human rights and the concepts of personality, integrity and self-determination of individuals. Evaluation of the appropriateness of the technology through involvement of stakeholders in all phases of HTA (social desirability) is considered as one of the main components of HTA.	None	(53)
Thailand/ HiTAP, iHPP				
Thai HTA guidelines	2008	The guidelines suggest consideration of equity issues and their integration with results of economic evaluation by choosing appropriate evaluation techniques and using ethical criteria and social preferences in health resource allocation decisions and priority setting.	None	(58)
UK/NICE				
Social value judgments for HTA guidance	2008	The document includes both general and case-specific social value judgments and asks NICE's advisory bodies to take into account ethical principles of respect for autonomy, non-maleficence, beneficence, and justice (distributional and procedural), fundamental operating principles (legal and procedural) in appraising health care technologies.	None	(54)
Guide to methods of technology appraisal	2008	In addition to appraisal of evidence on clinical-and cost-effectiveness, the guidelines encourage consideration of evidence related to acceptability, appropriateness, preference, equity and equality.	None	(55)

AHTAPol= Agency for Health Technology Assessment Poland; CADTH= Canadian Agency for Drugs and Technologies in Health; DACEHTA= Danish Centre for Evaluation and Health Technology Assessment; DAHTA= German Agency for HTA; DIMDI=German Institute for Medical Documentation and Information; ECHTA= European Collaboration for Health Technology Assessment; EUnetHTA= the European Network for Health Technology Assessment; GmbH= Gesundheit Österreich; HIQA= Health Information and Quality Authority; HITAP= Health Intervention and Technology Assessment Program (Thailand); HTA= health technology assessment; iHPP= International Health Policy Program (Thailand); INAHTA= International Network of Agencies for Health Technology Assessment ;INNOVAL= Institute for innovation and valuation in health care; KCE= Belgian Health Care Knowledge Centre; NICE= NHS National Institute for Clinical Excellence; NOKC= Norwegian Knowledge Centre for the Health Services ; SBU= Swedish Council on Technology Assessment in Health Care ; SWOT= strengths, weaknesses, opportunities and threats analysis; UETS= Unidad de Evaluacion de Tecnologias Sanitarias ; UK= the United Kingdom; WHO= World Health Organization

Supplementary Material 1- Search strategy

DATABASES

Embase <1980 to 2013 Week 22> ; Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> ; PsycINFO <1806 to June Week 1 2013>; PubMed <up to June 1st 2013>; Wiley's Cochrane Library <up to June 1st 2013>; and the Centre for Reviews and Dissemination's (CRD) HTA database <up to June 1st 2013>

Monthly search updates began July 1st 2013 and ran until October 1st 2013.

Strategy:

#	Searches	Results
1	(health technology assessment? or HTA? or ((new or emerg*) adj3 technolog*)).ti,ab.	72381
2	(ethics or ethical* or moral* or bioethic*).mp.	410599
3	(humanism or dignity or integrity or human right* or principlism or normativ* or principle-base* or beneficence or autonomy or non-maleficence or philosoph* or aristoteles or socrates or justice or fairness or hope or accessible or accessibility or Beauchamp or childress or equilibrium* or wide reflective* or socratic or social shaping or casuistry or coherence analy* or eclectic* or right to die or right to life or social value* or ethnic value* or personal value* or harm or benefit-harm or harm-benefit or elsi or elsa).ti,ab,ot.	1555051
4	(framework? or guide? or guideline? or method? or methodolog* or meta-methodolog* or metamethodolog* or tool* or toolkit* or tool-kit* or procedure?).mp.	12515142
5	[or/2-3]	1939464
6	[1 and 4 and 5]	1847
7	[remove duplicates from 6]	1359

Syntax guide:

*=   a truncation symbol (wildcard) to retrieve plurals or varying endings

?=   a truncation symbol for one or no characters only

.ab=   abstract

adj#=   Adjacency within # number of words (in any order)

.kw=   Medline=Keyword Heading; contains the Keyword Headings assigned by indexers at the National Library of Medicine to describe the content of an article

Embase=Key Word; contains keywords defined by the author of the article

.mp=   Medline: title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, unique identifier

Embase: title, abstract, subject headings, heading word, original title, keyword

.ti=   title

GREY LITERATURE:

Websites of Health Technology Assessment Agencies

Country	Agencies
Inter/Multi National	International Network for Agencies for Health Technology Assessment (INAHTA); Health Technology Assessment International (HTAi); International Society For Pharmacoeconomics and Outcomes Research (ISPOR); WHO Health Evidence Network; European Information Network on New and Changing Health Technologies (EUROSCAN). University of Birmingham. National Horizon Scanning Centre; European network for health technology assessment (EUnetHTA)
Australia	Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S); Centre for Clinical Effectiveness, Monash University; Medicare Services Advisory Committee, Department of Health and Aging
Austria	Institute of Technology Assessment (ITA); Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA)
Belgium	Federal Kenniscentrum voor de Gezendheidszorg (KCE)
Canada	Canadian Agency for Drugs and Technologies in Health (CADTH); Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS). Québec; Centre for Health Services and Policy Research, University of British Columbia; Institute for Clinical Evaluative Sciences (ICES). Ontario; Institute of Health Economics (IHE). Alberta; The Technology Assessment Unit of the McGill University Health Centre
China	National Health Development Research Center (NHDRC); Key Lab of Health Technology Assessment
Croatia:	Agency for Quality and Accreditation in Health Care
Denmark	Danish Centre for Evaluation and Health Technology Assessment (DCEHTA); Danish Institute for Health Services Research and Development (DSI)
Finland	Finnish Office for Health Care Technology and Assessment (FinOHTA).
France	L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES). Ministere de la Santé, de la Famille, et des Personnes handicappés; Committee for Evaluation and Diffusion of Innovative Technologies (CEDIT); French National Authority for Health (HAS) Department of Economics and Public Health Assessment
Germany	German Institute for Medical Documentation and Information (DIMDI)
India	Indian Institute of Health Management Research (IIHMR)
Israel	Israel Center for Technology Assessment in Health Care (ICTAHC)
Japan	National Institute of Public Health/ Department of Technology Assessment and Biostatistics
Malaysia	Ministry of Health/ Health Technology Assessment Unit
Netherlands	College voor Zorgverzekeringen/Health Care Insurance Board (CVZ); Health Council of the Netherlands
New Zealand	New Zealand Health Technology Assessment Clearing House for Health Outcomes and Health Technology Assessment (NZHTA)
Norway	Norwegian Centre for Health Technology Assessment (SMM)
Poland	Agency for Health Technology Assessment (AHTAPol)

South Korea	National Evidence-based Healthcare Collaborating Agency (NECA); Ministry of Health/ Health Insurance Review & Assessment Agency (HIRA);
Spain	Agencia de Evaluación de Tecnologias Sanitarias (AETS), Instituto de Salud "Carlos III"/ Health Technology Assessment Agency, Basque Office for Health Technology Assessment (OSTEBA); Catalan Agency for Health Technology Assessment and Research (CAHTA)
Sweden	Centre for Medical Technology Assessment (CMT); Swedish Council on Technology Assessment in Health Care (SBU)
Switzerland	Swiss Network for Health Technology Assessment; Institute for Innovation and Valuation in Health Care (INNOVAL)
Taiwan	Center for Drug Evaluation (CDE)
Thailand	Health Intervention and Technology Assessment Program (HiTAP)/ International Health Policy Program (iHPP)
UK	National Horizon Scanning Centre (NHSC); NIHR Health Technology Assessment programme, Coordinating Centre for Health Technology Assessment (NCCHTA); NHS National Institute for Clinical Excellence (NICE); NHS Quality Improvement Scotland; University of York NHS Centre for Reviews and Dissemination (NHS CRD)
USA	Agency for Healthcare Research and Quality (AHRQ); ECRI Institute; Institute for Clinical Systems Improvement (ICSI); Blue Cross and Blue Shield Association's Technology Evaluation Center (TEC)

Search Engine

Google

http://www.google.ca/

CHAPTER 3

Barriers and facilitators influencing ethical evaluation in health technology assessment[†]

Short Title: Factors Influencing Ethical Analysis in HTA

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URL: http://journals.cambridge.org/abstract_S026646231500032X

Abstract

Objective: The objective of this study was to explore barriers and facilitators influencing the integration of ethical considerations in health technology assessment (HTA).

Methods: The study consisted of two complementary approaches: (a) a systematic review of the literature; and (b) an eighteen-item online survey that was distributed to fifty-six HTA agencies affiliated with the International Network of Agencies for Health Technology Assessment.

Results: The review identified twenty-six relevant articles. The most often cited barriers in the literature were: scarcity, heterogeneity and complexity of ethical analysis methods; challenges in translating ethical analysis results into knowledge that is useful for decision-makers; and lack of organizational support in terms of required expertise, time and financial resources. The most frequently cited facilitators included: usage of value-based appraisal methods, stakeholder and public engagement, enhancement of practice guidelines, ethical expertise, and educational interventions.

Representatives of twenty-six (46.5 percent) agencies from nineteen countries completed the survey. A median of 10 percent (interquartile range, 5 percent to 50 percent) of the HTA products produced by the agencies was reported to include an assessment of ethical aspects. The most commonly perceived barriers were: limited ethical knowledge and expertise, insufficient time and resources, and difficulties in finding ethical evidence or using ethical guidelines. Educational interventions, demand by policy-makers, and involvement of ethicists in HTA were the most commonly perceived facilitators.

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Conclusions: Our results emphasize the importance of simplification of ethics

methodology and development of good practice guidelines in HTA, as well as capacity-

building for engaging HTA practitioners in ethical analyses.

Keywords: Health technology assessment; Ethical analysis; Barriers; Facilitators; Survey

Acknowledgements:

Introduction

Health technology assessment (HTA) is a policy tool that helps decision-makers understand the potential impacts of implementing a healthcare technology through a comprehensive evaluation of its clinical, economic, social, ethical, and legal implications (1). By doing so, HTAs reduce decision uncertainties and help facilitate the decision-making process. Because novel technologies may create some ethical and moral issues, HTAs can be less useful for decision making if they fail to systematically and objectively consider the ethical issues that might lead to different decisions, or if they do not represent moral values that may have an impact on dissemination and implementation of new health technologies (2). In a survey of HTA decision makers in thirteen European countries, fifteen out of the eighteen respondents (83 percent) perceived ethical issues as being moderately to highly influential on their decisions about health technologies (3).

Despite the increasing emphasis on the importance of ethical assessment as a part of the HTA process, priority-setting and policy making for new heath technologies in most jurisdictions rely mainly on the assessment of clinical- and cost-effectiveness of health technologies. Ethical considerations around the technology are usually absent or poorly addressed in the majority of HTA reports. A systematic review conducted by the Institute of Health Economics (Canada) to describe the criteria used by major publicly funded HTA agencies to set priorities for HTA revealed that less than 20 percent of the agencies considered ethical implications of health technologies in priority setting (4). There have also been several studies in the literature which show that only a small proportion of

HTA products address equity considerations (5-7) or wider ethical and social issues as a part of the assessment process (8-13).

In response to the recognition of a need for a structured methodology for ethical analysis in HTA by producers and users of HTA products(14-16), several frameworks, models, and evaluation tools have been proposed by several authors (17). However, their use has been constrained most likely due to practical issues. The results of a survey of the International Network of Agencies for Health Technology Assessment (INAHTA) member agencies in 2003 indicated that the majority of the respondent organizations did not have an internal system for handling ethical issues as a part of HTA (18). Other reasons have also been stated in the literature for a lack of consideration of ethical issues in HTA practice including: diversity of the available methodologies and lack of consensus on a practical method for considering ethical issues in HTA (16;19), limited information on the appropriate scope and level of details of an ethical analysis in HTA (15;16), HTA professionals' attitudes toward the inclusion of ethical considerations in HTA (19), and uncertainties around the role of ethics expertise in such analyses (15). However, to the best of our knowledge, no studies have been published which have formally evaluated the factors that might influence the intention of HTA procedures to perform an ethical analysis.

A need for identifying barriers and enablers to the use of existing guidelines and tools for ethical evaluation in HTA has been highlighted by experts in the field of ethics and HTA

(20). Understanding the ways in which ethical evaluation is performed by HTA producers and identifying related barriers and facilitators can be regarded as important steps toward selecting or tailoring a practical framework to promote ethical analysis in HTA, and thereby to enhance the value of HTA as a policy making research tool. This study will address this need by identifying key barriers that inhibit as well as facilitators that improve successful incorporation of ethical consideration in HTA.

Methods

Two complementary approaches were undertaken: (a) a systematic review of the literature to identify the range of themes on barriers and facilitators to the incorporation of ethical issues in HTA; and (b) an international survey to explore the degree to which and how HTA agencies include ethical considerations in their HTA products, and to identify key enablers and challenges around their adoption of ethical analysis methods.

Systematic review of literature

Structured literature searches were conducted across the following databases to identify English-language articles that reported or provided insights on barriers and/or facilitators of ethical evaluation in HTA: Ovid's Medline (In-Process & Other Non-Indexed Citations) and EMBASE; PubMed (for non-Medline records only); and Wiley's Cochrane Library, including: Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Methodology Register, and HTA Database. Separate searches were also conducted in Bioethics Literature Database (BELIT) and the

European Database on Literature of Ethics in Biotechnology (ENDEBIT) through Ethicsweb database search interface. The searches used a combination of the National Library of Medicine's Medical Subject Heading (MeSH) terms and keywords for the concepts of "health technology assessment", ethics, barriers (or synonyms) and enablers (or synonyms). No restriction on year of publication was applied. Adaptations were made in the search strategy to comply with the requirements of each database. The searches were initially undertaken between February and April 2013, and subsequently updated in April 2014. Additional literature was sought from Web sites of international HTA organizations, the reference lists of the included studies, and the commentaries or discussion papers suggested by experts in the field. The details of the search strategy are provided in the Supplementary Material 1.

Decisions on the relevance of the identified citations were made independently by two reviewers. Studies were included if they were quantitative or qualitative studies, published in English, that investigated or discussed the factors affecting the integration of ethical considerations in HTA. A thematic analysis of data was undertaken, through which the articles were read repeatedly; then similar concepts on barriers to or facilitators of ethical evaluation were abstracted and grouped together to determine common themes present in the included studies. Data abstraction was performed by one reviewer and checked by a second. Any discrepancies were resolved by discussion.

Survey of HTA agencies

A Survey, consisting of eighteen predominantly multiple-choice questions, was designed specifically for this study using preliminary results of the systematic literature review and in consultation with experts in the fields of HTA and ethics. The survey was in English and included general information about the respondent and the HTA agency, questions related to the current situation of handling ethical issues in HTA reports produced by the agency, and questions regarding factors influencing incorporation of ethical issues in HTA. The survey asked respondents to answer the questions from their organization's point of view. A five-point Likert scale was used in two questions as a rating tool. The rest of the questions asked respondents to pick the best answer or answers from among the provided options. An "other" option was included for respondents' additional free-text information. Two questions asked for electronic links or references to any existing written instructions or guidelines being used by the HTA organization. The questionnaire was pretested with five potential respondents to ensure face validity and technical functioning. Feedback from the pretest respondents were used to modify the final version of the survey. Ethics approval for the survey was acquired from McMaster University's Research Ethics Board. The survey questionnaire is available in the Supplementary Material 2.

A link to the survey was sent, through an e-mail invitation, to all of the HTA agencies affiliated with the International Network of Agencies for Health Technology Assessment (INAHTA). At the time of the study (April 2013), this network consisted of fifty-six

HTA-producer agencies from thirty-one countries in North and Latin America, Europe, Africa, Asia, Australia, and New Zealand. Heads of the HTA agencies or their designated representatives were identified by accessing the Web sites of all of the fifty-six INAHTA member agencies. The recipients were asked to complete the survey questionnaire by following the provided link to the survey (through the Survey Monkey Internet Web service) (21), or to forward the email to the most appropriate person in the agency to respond. Two reminder emails were sent to maximize the response rate.

A descriptive analysis of the survey data was conducted to describe the characteristics of the participating HTA agencies, their experiences with addressing ethics in HTA, and their perceived barriers and facilitators.

Results

Systematic review

Included studies

The search resulted in 495 citations, 65 of which were selected for full text review. Ultimately, a total of twenty-six articles met the inclusion criteria and were used in this review. Details of the study selection process are outlined in Figure 1.

Of the included studies, only one was explicit in its focus on the assessment of barriers and facilitators to the incorporation of ethical aspects in the assessment of healthcare interventions (22). The remaining studies discussed barriers and facilitators qualitatively

through critical discussions (23-34), philosophical analysis of ethical methodologies or case studies (15;16;35-38), content analysis of HTA reports (9;39), and collecting expert opinion by means of surveys, focus group discussion, or expert workshop discussions (22;40-43). The barriers and facilitators identified in our review are described below.

Barriers and facilitators

Table 1 summarizes a range of barriers and facilitators to ethical considerations in HTA which were cited by the included studies. It can be seen from the table that the barriers were more frequently cited than the facilitators. Of the twenty-six included studies, twenty-three identified barriers (9;14-16;22-33;36-41;43) and ten identified facilitators (15;25;32-34;37;39;41-43) of ethical analysis in HTA. Through a thematic analysis, we categorized factors specified as barriers or facilitators into five themes pertaining to: methodology of ethical evaluation, technological context, HTA organization, HTA-practitioners, and HTA policy-making. Within each theme, the identified factors were further organized into specific sub-themes. For example, those relating to the methodology of ethical evaluation were classified as: focus of analysis, methodological guidelines, appropriateness of analysis to the context, level of complexity, and validity of method; or individual barriers and facilitators associated with HTA practitioners were classified as their knowledge, attitude, or practice.

The most often cited barriers were scarcity, heterogeneity and complexity of ethical analysis methods; challenges in translating ethical analysis results into knowledge that is

useful for decision makers; lack of organizational support in terms of required expertise, time and financial resources. Other barriers included the diversity in requirements and policies of HTA agencies, technical focus of commonly used ethical evaluation methods, lack of rigorous methods for validation of ethical frameworks for HTA, negative attitudes of HTA practitioners toward inclusion of ethical considerations in the assessment process, and poor knowledge and limited training of HTA practitioners with ethical analysis methods.

The most commonly cited facilitators included usage of value-based appraisal methods in HTA rather than science-based assessments, using stakeholder dialogue, including policy makers and general public, as a source of data for ethical analysis, development of generic ethical appraisal tools and practice guidelines, using appropriate ethical expertise, and training HTA practitioners with social and ethical analysis methods.

Survey of HTA agencies

Directors or representatives of thirty-one out of fifty-six HTA agencies responded to the survey invitation; however, two of those were unable to participate, due to their busy schedules, and three failed to complete the online questionnaire, leaving a sample of participants from twenty-six HTA agencies (a response rate of 46.5 percent). The majority of responding agencies were from Europe, including two agencies each from Germany, Spain, Italy, the Netherlands, and the United Kingdom; and one agency each from Austria, Sweden, Norway, Poland, Finland, Scotland, Belgium, and Lithuania.

Other participating agencies were located in Canada (three agencies), South Africa, Australia, Brazil, Malaysia, and Taiwan (one agency each). Four of the HTA agencies were academic research institutions, five were departments of government ministries (mainly ministries of health), and fifteen were governmental or quasi-governmental agencies. Quasi-governmental agencies are privately-managed organizations that are supported by governmental funding. A lower proportion of the survey participants were from hospital HTA units (one agency) or independent HTA agencies (one agency). The participants consisted of heads of HTA agencies or units (42.3 percent), program managers (11.5 percent), and HTA researchers (46.2 percent).

Medical devices and procedures were the most common technologies covered by the HTA agencies (100 percent and 92 percent, respectively), followed by public health interventions (69 percent), pharmaceuticals (58 percent) and health system interventions (58 percent). More than 80 percent of the agencies produced full HTA reports and rapid assessments. The median number of published assessments for each of these agencies in one year was reported to be five (interquartile range [IQR] 1 to 10) for HTA reports and five (IQR 1 to 20) for rapid assessments. About 50 percent of the agencies performed systematic reviews, with a median of one (IQR 0 to 4) per year. More details about the characteristics of the respondent agencies are provided in the Supplementary Material 3.

The following presents the reported practice of addressing ethical aspects amongst the surveyed HTA agencies; as well as perceived barriers and facilitators of representatives of such agencies regarding incorporation of ethics in HTA.

Assessment of ethical issues in HTA

Based on the survey findings, a median of 10 percent (IQR 5 percent to 50 percent) of the HTA products produced by the agencies included an assessment of ethical aspects, regardless of what their definition of ethics might be, and a median of 5 percent (IQR 0 percent to 40 percent) considered only equity aspects. Two of the European HTA agencies (the German Agency for Health Technology Assessment (DAHTA), and the Swedish Council on Health Technology Assessment (SBU)) reported that 100 percent of their HTA reports included an assessment of ethical issues. However, no consistent patterns were found to indicate that inclusion of ethical issues in HTA varied across different types of agencies or various geographic regions. Respondents from ten HTA agencies (39 percent) reported that their organization gave a high or very high priority to the consideration of ethical issues, while thirteen agencies (50 percent) assigned a low (five agencies) or medium (eight agencies) level of priority to the ethical aspects of health technologies. In the remaining three agencies (11 percent) no priority was assumed for ethical aspects.

In response to the question that asked respondents to indicate who in their organization was responsible for the incorporation of ethical issues, 8 percent believed that this

question was not applicable to the types of reports made by their agencies, 77 percent mentioned that a team of HTA professionals, not including an ethicist, was responsible to address ethical considerations, if needed. In 15 percent of the agencies, ethical evaluations were typically performed by individual ethicists or multi-disciplinary teams including ethicists. All but one of these agencies reported that they depended on externally recruited ethical expertise.

Seven of the twenty-six respondents (27 percent) indicated that written instructions on how to address ethical issues around health technologies were used in their organizations; of those, three reported to have internal checklists, two used the European Network for Health Technology Assessment (EUnetHTA)'s HTA Core Model (44), and two used various published frameworks or tools including Hofmann's thirty-three morally relevant questions (14) and the HTA Core Model (44). Eight agencies (30 percent) stated that their agency had a guidance document in preparation that would serve this purpose. The remaining agencies did not have any instructions for addressing ethical considerations. Figure 2 shows how the respondents rated the usefulness of existing ethical frameworks or guidelines. It is notable that more than 20 percent of the survey participants were not aware of any published guidance documents that could be useful for ethical evaluation in HTA.

Perceived barriers and facilitators to incorporation of ethics in HTA among the surveyed agencies

When asked what barriers might discourage HTA professionals from addressing ethical issues in their assessments, the most frequently reported barriers were: limited ethical knowledge and expertise of HTA producers, lack of sufficient time and resources, scantness of useful evidence concerning ethical aspects of health technologies, problems in identifying and using the existing ethical guidelines, and conflicting policies and rules. The respondents also identified a number of other obstacles that were not listed in the questionnaire, such as lack of organizational requirements and negative attitudes of HTA professionals towards assessment of ethical aspects (Figure 3A).

We also asked representatives of the HTA agencies about what would help or encourage them to apply ethical evaluation methods in their assessments. More than 50 percent of the respondents perceived educational sessions, demand by policy makers, and involvement of ethicists in the HTA process as the key facilitators. Stakeholder engagement, improvement of existing guidance documents, and public pressure were reported to be other important drivers of ethical analysis in HTA. The participants also identified additional motivators in the free text section, such as practical examples to aid ethical assessment and availability of sufficient resources (Figure 3B).

Discussion

In this study we aimed to understand the factors that may influence the incorporation of ethics in HTA by drawing on existing literature and through the survey of national and international HTA agencies. Overall, there was a close agreement between the survey and the review findings and the results seemed to reinforce each other. However, discussions in the literature mostly focused on the adequacy and quality of methodological documents, while the survey participants more frequently perceived lack of resourcing and lack of required knowledge and skills as important obstacles to evaluation of ethical issues.

Based on the results of our survey, close to 90 percent of the HTA agencies assigned some level of priority to the inclusion of ethical considerations in HTA; although, a relatively small proportion of them incorporated relevant ethical analysis methods in their assessments. While it was clear that the HTA agencies struggled with providing adequate ethical analysis due to several potential barriers, which will be discussed below, we are optimistic and encouraged by their expressed level of intention for considering ethical issues in HTA.

Our study identified the diversity and complexity of ethics methods and the lack of practical guidelines as important challenges in pursuing ethical analysis. Conducting an ethical analysis is quite complex in nature, requires advanced skills, and can be difficult to perform within the frameworks of the majority of existing HTA agencies (44). Adding

to this complexity is the fact that several frameworks utilizing varied analytic methods have been proposed for this purpose (17). In other words, no 'one-size-fits-all' method exists for ethical analysis. Of interest, our survey revealed that approximately one in four respondents were unaware of existing ethics guidelines in HTA. Lack of awareness can be considered a technical barrier to using the guidelines. In addition, a negative attitude toward the usefulness of the existing guidance documents, which was present in a small number of the survey participants, can act as a cognitive barrier. These would suggest an essential role for effective methods for identifying knowledge gaps as well as for training programs that are specifically designed for HTA teams to help them evaluate normative considerations around healthcare technologies.

Lack of familiarity with the complex philosophical theories and ethical reasoning methods was frequently cited as a barrier which may restrict HTA-practitioners' ability or affect their willingness to be involved in ethical analyses. HTA professionals can only take ethical considerations into account in their products if they can reflect on them. In an international survey on the attitudes of HTA professionals toward ethical analysis in HTA, the majority of respondents agreed that incorporation of ethical issues was important, and that ethical recommendations should be included in HTA reports in a normative (45 percent) or descriptive (38 percent) manner. Despite this positive attitude, the respondents of this survey believed that ethical analysis should be performed by an ethicist (68 percent) or an external consultant (78 percent)(19). We suggest that future research should focus on factors that influence HTA-practitioners' ability and desire to

undertake ethical evaluations, and address how and to what extent ethical evaluations can be undertaken by non-ethicist HTA professionals.

Organizational factors such as lack of required knowledge and skills, short project time frames and insufficient financial resources were commonly highlighted in the literature as well as by the survey respondents as important barriers to implementing ethics in HTA. Addressing ethical issues can also be affected by the HTA organizations' culture and the practical frameworks within which they operate. HTA agencies that set a low priority on ethical evaluation are less likely to be willing to provide initiatives to address ethical issues. In addition, a favorable organizational environment is required for conducting ethical evaluations. The Dominance of scientific and technical culture (leadership and expertise) in some HTA agencies may lead to the perception that ethical analyses do not fit or are not feasible in HTA practice (45). While we believe no conflict exists between technical and ethical concerns, we acknowledge that HTA producers with clinical or economic research backgrounds tend to subscribe to a distinction between empirically "verifiable" facts and "unverifiable" normative aspects or value judgments; and because ethics is often understood to be exclusively a normative domain, they might be reluctant to incorporate ethical aspects of healthcare technologies into their assessments.

The results of our study suggest that training and capacity-building in ethical methods is crucial in implementing ethics into HTA. We believe that there is an unmet need not only to develop internal capacity in HTA organizations, but also to identify suitable

mechanisms to exchange ethics-specific knowledge and experience among different organizations. Availability of appropriate ethical expertise was found to be another critical success factor. The review results suggest that experts who contribute to ethical analysis in HTA require not only a thorough knowledge in ethical principles and reasoning, but also enough background information about the technological context and HTA process (15;35;42).

The agencies surveyed also perceived good practice guideline development as an important facilitator that could enhance the use of ethical evaluation methods in HTA. Although efforts have been directed towards development of practical methods to help support HTA professionals in performing ethical analysis (17;20;46), a lack of awareness and familiarity with the guidelines and an uncertainty about their usefulness seem to exist among HTA producers. In our survey, more than a quarter of the responding agencies were not aware of any guidance documents for addressing ethical issues or found the existing ethical guidelines and frameworks not useful. Lack of awareness and lack of familiarity can be improved through professional and continuing education; however, more research is needed to investigate the reasons that might explain the lack of perceived usefulness of ethics guidelines among HTA professionals.

Enhancing ethical understanding through stakeholder engagement was another facilitator that was identified in both the survey and literature review components of our study. The topic of stakeholder engagement in HTA has received great attention in recent years

(32;43;47;48). The identification and inclusion of stakeholders can be an important step in anticipating, and addressing ethical issues in HTA. However, to make high quality decisions that reflect values and preferences of a broad range of stakeholders, there needs to be some mechanisms developed to sufficiently inform stakeholders about the technology and its potential positive and negative impacts.

While the key barriers to and facilitators of ethical evaluation identified in this study may provide directions for future research and development, we recognize that our study has some limitations. First, there is a risk of bias in our systematic review due to the fact that only English-language studies were included. Second, the survey may potentially be subject to selection bias due to nonresponse. Although the response rate for our survey (46.5 percent) is noticeably lower than the 92 percent response rate achieved by the INAHTA Secretariat's survey on ethical issues in 2003 (18), it exceeds those of similar surveys which targeted major international HTA agencies(11;19;49;50). The study by Baruch and Holtom shows that response rates from representatives of organizations are, on average, lower than those from individuals (37.2 percent vs. 52.7 percent)(51). This study also suggests that response enhancing techniques, such as reminders, can be less effective in increasing response rates at the organizational level where managers and executive employees are being surveyed. Third, while it was beyond the scope of the present study to explore the true definition and principles of ethical evaluations performed by the surveyed HTA agencies, it appears likely that the expressed barriers and facilitators might have been affected by the respondents' perceptions of ethical

concepts (e.g., equity, respect, rights or duties) and the ways in which they would choose

to address them. The survey responses might also have been affected by respondents'

personal interests, their role in the organization, their educational background, or their

tendency to provide favorable responses. Therefore there is a possibility that information

bias could have been introduced into our study. It may be useful to perform

supplementary qualitative research to gain more information on the actual practices of

different agencies regarding ethical evaluation of healthcare technologies and barriers and

facilitators that they encounter in their routine practice.

Finally, our survey was an exploratory effort to provide a descriptive analysis of

expressed attitudes, practices, and experiences of HTA producers regarding evaluation of

ethical issues. However, the questions remain as to how ethical analyses are integrated in

the HTA agency's routine practice and whether such analyses are able to incorporate an

important impact on policy decisions.

Conclusion

The current study highlights potential facilitators that could enhance the use of ethical

evaluation methods, and specific barriers that need to be overcome in order to increase

the success of ethical evaluations in HTA. Based on our results, specific consideration

should be given to: simplification of ethics methodology in HTA through adaptation of

procedural guidelines or tools that are routinely used in other domains of the HTA

process; capacity-building through development of educational materials, and providing

case studies to acquaint HTA professionals with the process of ethical analysis, as well as strengthening skills and motivations of HTA producers in the field of ethics; development of good practice guidelines for ethical evaluation of healthcare technologies; and usage of deliberative approaches in HTA.

Challenges that stem from organizational factors, especially insufficient resources, also seem to be of importance. Suitable mechanisms should be sought at organizational levels to overcome these challenges for the purpose of effectively incorporating ethical aspects into HTA.

It is debatable that a certain level of standardization may be desirable to improve the rigor of ethical evaluations in HTA and to assist reviewers and end-users of HTA products in assessing the quality and reliability of the ethical evaluation process.

Conflict of Interest

The authors have no conflict of interest to declare.

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Figure 1 - Study selection flow chart
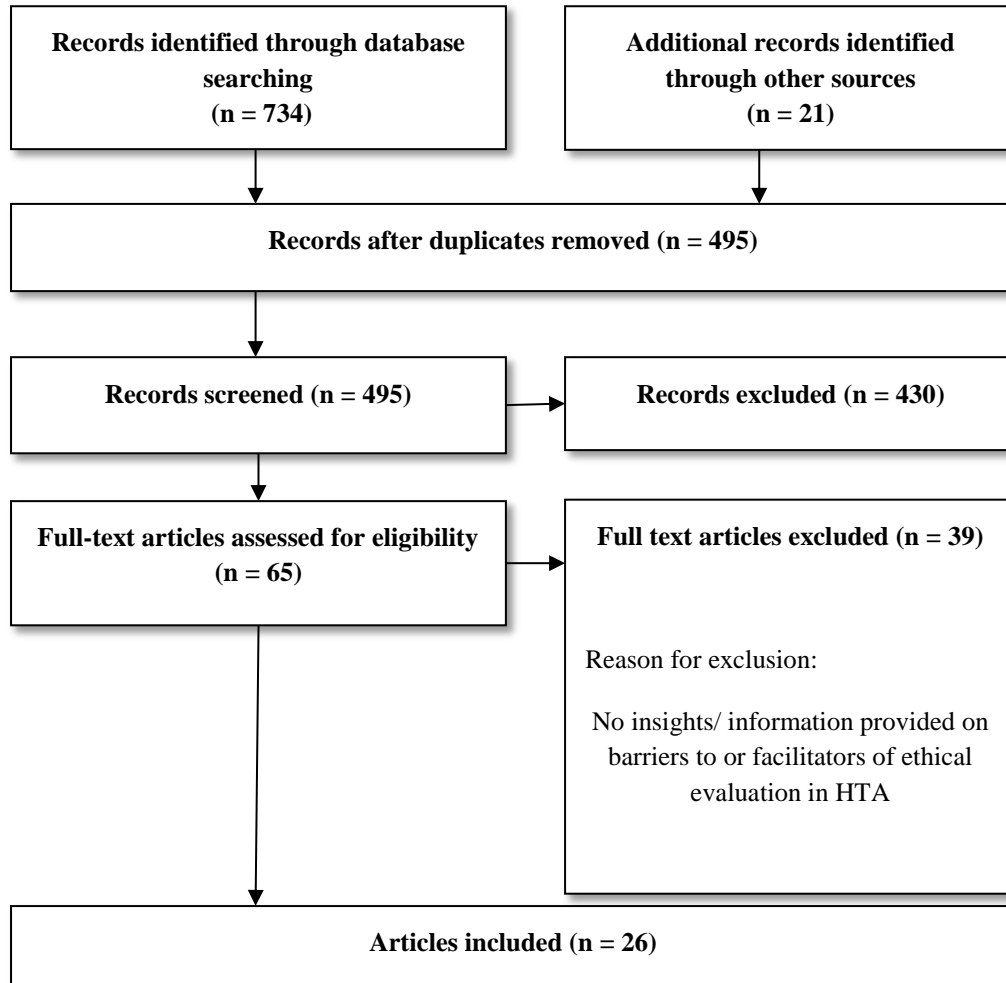
Figure2 - Survey participants' perception of usefulness of existing ethical guidance documents (n=26)
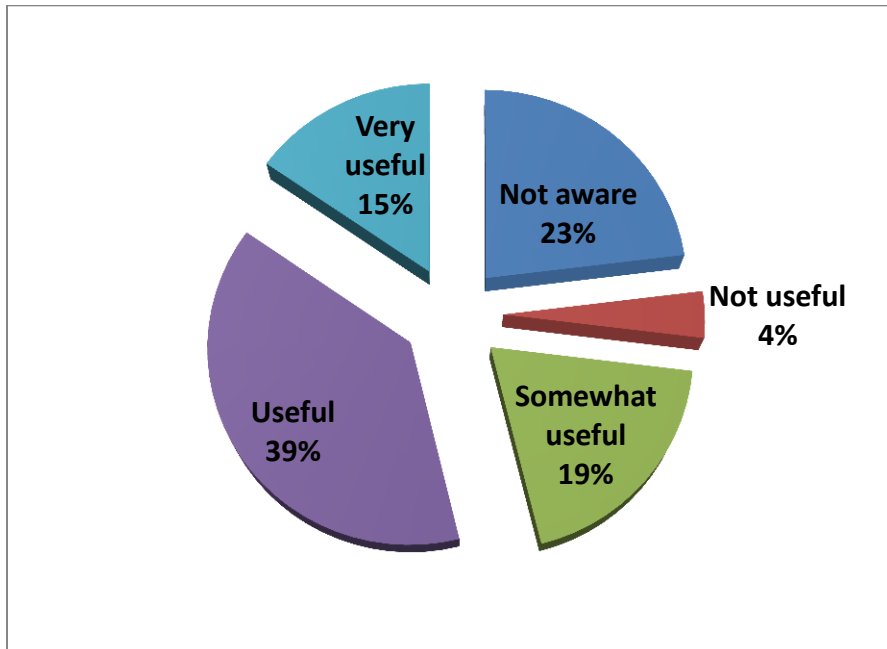
Figure3 - Survey participants' perceived barriers to and facilitators of the incorporation of ethical considerations in HTA (n=26)

3A. perceived barriers of ethical analysis in HTA

3B. perceived facilitators of ethical analysis in HTA
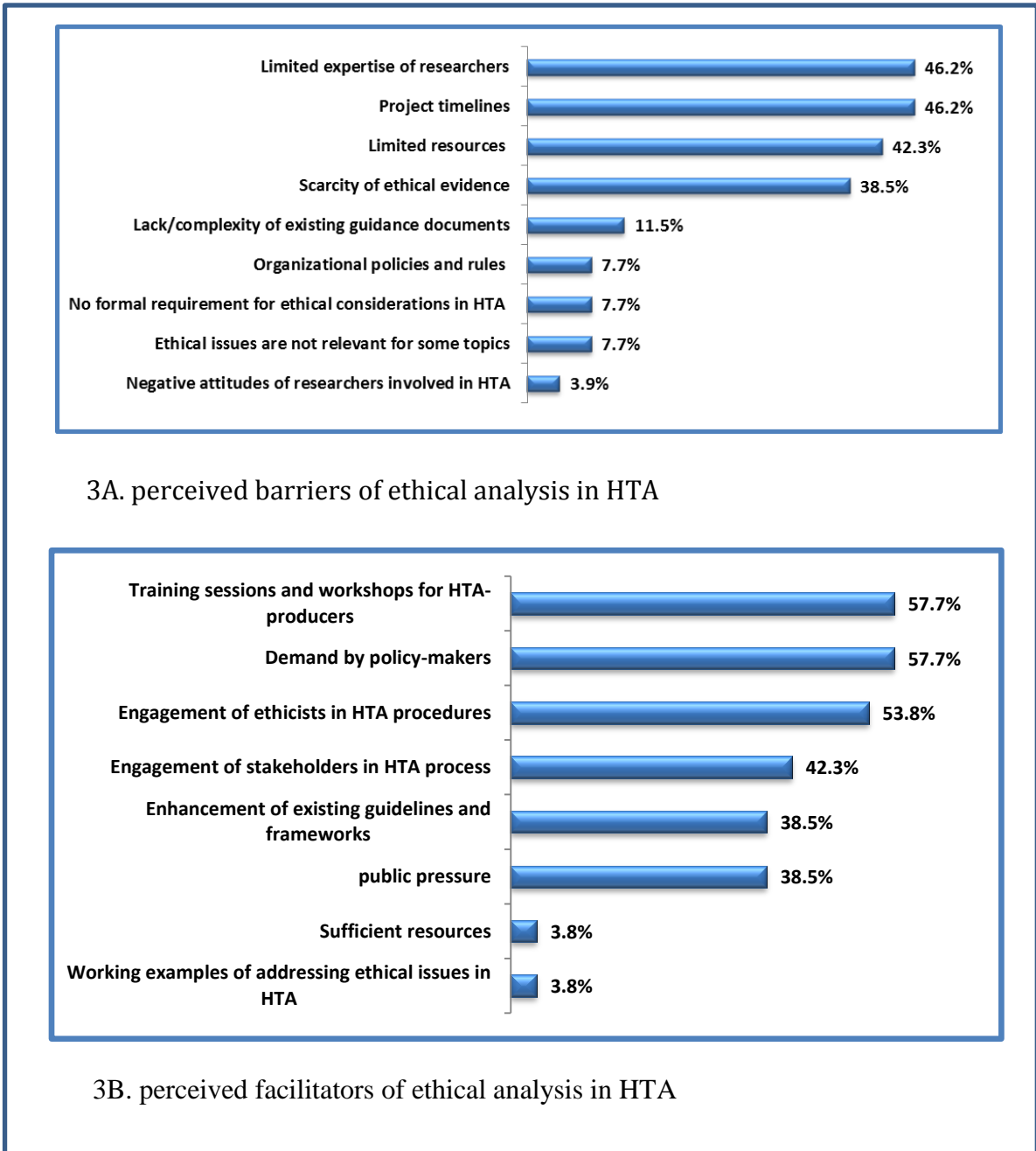
Table 1 - Key barriers and facilitators identified by the studies included in the systematic review

Themes	Barriers		Facilitators	
	Indications	**Number of studies**	**Indications**	**Number of studies**
Methodology of ethical evaluation				
Goal / focus of analysis	— Technical orientation and narrow focus of proposed ethical analysis methods for HTA (29-31) — Limiting rationality to descriptively manageable tools (31) — Procedural framing of ethical evaluation by mandatory institutions such as research or advisory committees (25)	4	— Making social and ethical dimensions explicit in HTA (39) — Choosing HTA frameworks that focus on 'appraisal' of technology and value judgments rather than 'assessment' of technology solely based on scientific evidence (33;34)	3
Methodological guidelines (quantity and quality)	— Underdeveloped ethical analysis methods (9;38;39;41) — Heterogeneity in ethical analysis methods (16;29) — Lack of consensus on methodology (16;26) — Lack of clarity and practical instructions (9;36;43) — Lack of practical methods which can be used by non-philosophers.(16) — Lack of methods which have been validated in HTA (25) — Shortcomings of ethical methods in self-criticism (30) — Lack of a systematic approach to the rigorous appraisal of ethics frameworks (28;33;37)	14	— Development of good practice guidelines and generic appraisal tools with sufficient information on sources of guidelines, development process, expertise of guideline authors, etc.(37;41) — Assignment of higher priority to qualitative research in HTA (41)	2
Level of complexity /practicality /appropriat eness	— Difficulty in managing moral challenges of a technology by one particular ethical approach (14) — Complexity involved in integrating or adapting theories and analytical tools (29;37;39;43) — Difficulties in defining values and dealing with value pluralism (38;39) — Complexity of the evaluation of the process, when ethical and social issues are added (28) — Challenges related to the collection and processing of ethics related (qualitative) data.(9;15;38) — Inappropriate use of ethical principles and theories(15;27)	10		0

Themes	Barriers		Facilitators	
	Indications	**Number of studies**	**Indications**	**Number of studies**
Technology				
Purpose and function	— Discounting the need for ethical analysis for minimally challenging technologies or the one that are less sensitive to social context (23;24;31)	3		0
HTA organization				
Requirements and policies	— Diversity in mandates of HTA organizations and their relationship to policy making (25;30;40)	3		0
Culture	— Lack of willingness to engage in ethical analysis (22) — Dominancy of technical and scientific culture (22;30;31;33) — The perception that decisions about ethical issues is the responsibility of other parties (22)	4		0
Resources: ethical expertise	— Limited access to ethics expertise in the field of HTA and health policy ethics (9;32;37;39) — Lack of expertise with complex ethical or social issues raised by the technology (22) — Unclear role of ethicists in HTA(9;15) — Insufficient educational efforts to develop ethical reasoning skills for healthcare researchers (22)	6	— Acknowledging and using appropriate ethical expertise for ethical analysis in HTA (15;42)	2
Resources: time and money	— Constraints on time, and financial resources (9;15;16;29;39)	5	— Availability of resources: time, money, and labor (32;43)	2
HTA Practitioners				
Knowledge	— Lack of awareness of there being ethical issues around the technology of interest (22) — Lack of familiarity with what ethical issues are referred to (22) — Limited training of HTA producers with ethical analysis methods (29)	2	— Training HTA-practitioners with social sciences and cultural studies (33) — Improved familiarity of ethicists involved in HTA with HTA and policy-making processes, as well as clinical and economic literature. (42)	2

Themes	Barriers		Facilitators	
	Indications	Number of studies	Indications	Number of studies
Attitude	— Perception that ethical issues are not relevant to the assessment (22;29) — The perception that ethical issues are not relevant to HTA (22) — The belief that ethical analysis may have a negative impact on the decisions related to a new technology (22) — The view that ethical issues are coextensive with legal and social issues (15) — Perception of lack of robustness associate with qualitative studies (43)	4		0
Practice	— Hesitation of HTA researchers to independently tackle ethical issues (22) — Lack of ethical reasoning skills (22)	1		0
HTA policy-making				
Goal of HTA policy-making	— Focus of HTA policy making on satisfying healthcare needs not health needs (26;34)	2	— Using public dialogue and stakeholder engagement approaches in HTA (25;32;43)	3
Usefulness of the ethical evaluation results for decision-making	— Making technology decisions on a "business-as-usual" basis without taking into account normative aspects of individual technologies (35) — Lack of demand for a comprehensive ethical assessment by decision makers (26) — Low utility for using a broad range of critical perspectives in HTA decision-making (25;36) — Difficulty of taking actions based on the results of ethical evaluations (14;15;25;35;36) — Lack of clarity about the ways in which ethical analysis should relate to policy (37;39) — Influence of "political dynamics" on the use of ethical analyses in policy-making (34)	9		0

Supplementary Material 1 - Search strategy

DATABASES

Ovid:
Embase <1980 to 2013 Week 22> ; Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> ; PsycINFO <1806 to April Week 2 2014>; Wiley's Cochrane Library <1st quarter 2014>; and the Centre for Reviews and Dissemination's (CRD) HTA database <1st quarter 2014>

PubMed:
PubMed <up to April 15th 2014>

Ethicsweb:
Bioethics Literature Database (BELIT)<up to April 2014>
European Database on Literature of Ethics in Biotechnology (ENDEBIT) <up to April 2014>

STRATEGY

1. (ethics or ethical* or moral* or bioethic*).mp.
2. (humanism or dignity or integrity or human right* or principlism or normativ* or principle-base* or beneficence or autonomy or non-maleficence or philosoph* or aristoteles or socrates or justice or fairness or hope or accessible or accessibility or Beauchamp or childress or equilibrium* or wide reflective* or socratic or social shaping or casuistry or coherence analy* or eclectic* or right to die or right to life or social value* or ethnic value* or personal value* or harm or benefit-harm or harm-benefit or elsi or elsa).ti,ab,kw.
3. 1 or 2
4. exp *Technology Assessment, Biomedical/
5. *Biomedical Technology Assessment/
6. (health technology assessment? or HTA? or ((new or emerg*) adj3 technolog*)).ti,ab.
7. 4 or 5 or 6
8. (barrier? or challenge? or enable* or facilitat* or obstacle? or inhibit* or promot*).mp
9. 3 and 7 and 8
10. remove duplicates from 9
11. limit 10 to English language

Syntax guide:
*=   a truncation symbol (wildcard) to retrieve plurals or varying endings
?=   a truncation symbol for one or no characters only
.ab=   abstract
adj#=   Adjacency within # number of words (in any order)
.kw=   Medline=Keyword Heading; contains the Keyword Headings assigned by indexers at the National Library of Medicine to describe the content of an article
            Embase=Key Word; contains keywords defined by the author of the article
.mp=   Medline: title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, unique identifier
            Embase: title, abstract, subject headings, heading word, original title, keyword
.ti=   title

GREY LITERATURE:

Websites of Health Technology Assessment Agencies

Country	Agencies
Inter/Multi National	International Network for Agencies for Health Technology Assessment (INAHTA); Health Technology Assessment International (HTAi); International Society For Pharmacoeconomics and Outcomes Research (ISPOR); WHO Health Evidence Network; European Information Network on New and Changing Health Technologies (EUROSCAN). University of Birmingham. National Horizon Scanning Centre; European network for health technology assessment (EUnetHTA)
Australia	Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S); Centre for Clinical Effectiveness, Monash University; Medicare Services Advisory Committee, Department of Health and Aging
Austria	Institute of Technology Assessment (ITA); Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA)
Belgium	Federal Kenniscentrum voor de Gezendheidszorg (KCE)
Canada	Canadian Agency for Drugs and Technologies in Health (CADTH); Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS). Québec; Centre for Health Services and Policy Research, University of British Columbia; Institute for Clinical Evaluative Sciences (ICES). Ontario; Institute of Health Economics (IHE). Alberta;The Technology Assessment Unit of the McGill University Health Centre
China	National Health Development Research Center (NHDRC); Key Lab of Health Technology Assessment
Croatia:	Agency for Quality and Accreditation in Health Care
Denmark	Danish Centre for Evaluation and Health Technology Assessment (DCEHTA); Danish Institute for Health Services Research and Development (DSI)
Finland	Finnish Office for Health Care Technology and Assessment (FinOHTA).
France	L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES). Ministere de la Santé, de la Famille, et des Personnes handicappés; Committee for Evaluation and Diffusion of Innovative Technologies (CEDIT); French National Authority for Health (HAS) Department of Economics and Public Health Assessment
Germany	German Institute for Medical Documentation and Information (DIMDI)
India	Indian Institute of Health Management Research (IIHMR)
Israel	Israel Center for Technology Assessment in Health Care (ICTAHC)
Japan	National Institute of Public Health/ Department of Technology Assessment and Biostatistics
Malaysia	Ministry of Health/ Health Technology Assessment Unit
Netherlands	College voor Zorgverzekeringen/Health Care Insurance Board (CVZ); Health Council of the Netherlands
New Zealand	New Zealand Health Technology Assessment Clearing House for Health Outcomes and Health Technology Assessment (NZHTA)
Norway	Norwegian Centre for Health Technology Assessment (SMM)

Poland	Agency for Health Technology Assessment (AHTAPol)
South Korea	National Evidence-based Healthcare Collaborating Agency (NECA); Ministry of Health/ Health Insurance Review & Assessment Agency (HIRA);
Spain	Agencia de Evaluación de Tecnologias Sanitarias (AETS), Instituto de Salud "Carlos III"/ Health Technology Assessment Agency, Basque Office for Health Technology Assessment (OSTEBA); Catalan Agency for Health Technology Assessment and Research (CAHTA)
Sweden	Centre for Medical Technology Assessment (CMT); Swedish Council on Technology Assessment in Health Care (SBU)
Switzerland	Swiss Network for Health Technology Assessment; Institute for Innovation and Valuation in Health Care (INNOVAL)
Taiwan	Center for Drug Evaluation (CDE)
Thailand	Health Intervention and Technology Assessment Program (HiTAP)/ International Health Policy Program (iHPP)
UK	National Horizon Scanning Centre (NHSC); NIHR Health Technology Assessment programme, Coordinating Centre for Health Technology Assessment (NCCHTA); NHS National Institute for Clinical Excellence (NICE); NHS Quality Improvement Scotland; University of York NHS Centre for Reviews and Dissemination (NHS CRD)
USA	Agency for Healthcare Research and Quality (AHRQ); ECRI Institute; Institute for Clinical Systems Improvement (ICSI); Blue Cross and Blue Shield Association's Technology Evaluation Center (TEC)

Search Engine
Google
http://www.google.ca/

Supplementary Material 2 - Survey questionnaire

Dear respondent,
This questionnaire will provide us with an understanding of your agency's experiences of handling ethical considerations in health technology assessment (HTA). Please ensure that your reply reflects the views of your organization.

A. Identification
A1. HTA agency:
A2. Country:
A3. Position of the respondent in the organization:
A4. Which of the following best describes your organization? (please select one) ☐ A governmental department ☐ A governmental/Quasi-governmental agency ☐ A research/academic institution ☐ Other (please specify): ……………………………
B. HTA procedures
B1. What kinds of health technologies does your organization mainly assess? (Please select all that apply.) ☐ Pharmaceuticals ☐ Diagnostic medical devices ☐ Medical procedures ☐ Public health interventions ☐ Health system interventions ☐ Other (please specify): ……………………………
B2. What types of reports/appraisals does your organization produce? (Please select all that apply.) ☐ Health technology Assessment report ☐ Rapid assessment/quick response service ☐ Technical queries ☐ Systematic reviews ☐ Horizon scanning ☐ Other (please specify): ……………………………
B3. Approximately how many of each kind of report/appraisal does your agency perform every year? ☐☐☐☐ Health technology Assessment report ☐☐☐☐ Rapid assessment/quick response service ☐☐☐☐ Technical queries ☐☐☐☐ Systematic reviews ☐☐☐☐ Horizon scanning ☐☐☐☐ Other (please specify): ……………………………

B4. What proportion of the reports/appraisals produced by your organization include assessment of:

□□□%	Clinical efficacy/effectiveness
□□□%	Safety
□□□%	Economic aspects
□□□%	Social aspects
□□□%	Ethical aspects (all ethical considerations)
□□□%	Ethical aspects (equity only)
□□□%	Legal aspects
□□□%	Organizational aspects
□□□%	Other (please specify): ……………………………

C. Consideration of ethical issues in HTA

C1. What level of priority does your organization currently assign to the consideration of ethical issues in HTA?
- □ Very high
- □ High
- □ Somewhat
- □ Low
- □ No priority

C2. In your organization, who is typically responsible for incorporating ethical considerations in HTA reports
- □ Ethicists
- □ Non-ethicists (please specify): ……………………………
- □ Multi-disciplinary team of researchers including an ethicist
- □ Multi-disciplinary team of researchers NOT including an ethicist
- □ Not applicable

C3. Does your organization have written instructions on how to address ethical issues in HTA reports?
- □ Yes   ▶ please answer C4
- □ No, in preparation   ▶
- □ No   ▶ please answer C5

C4. If you replied "Yes" to question C3, please provide a link to the document or give a reference for the document in the space below.
………
……

- □ Not willing to provide the document
- □ Not applicable

C5. If you replied "No" to question C3, please specify what types of methodological references would be considered by your organization when ethical issues are needed to be addressed?
- □ Published guidelines/frameworks
- □ Expert advice
- □ Both
- □ None

C6. Please provide, in the space below, references to the most frequently used guidance documents for addressing ethical issues in your organization:

……
……………………..
……
……………………..

☐ Not willing to provide references
☐ Not applicable

C7. How would you rate usefulness of the existing guidance documents?
☐ Very useful
☐ High
☐ Somewhat
☐ Low
☐ Not useful
☐ Not aware of any guidelines or frameworks

C8. When you recognize a need for ethical expert advice, where do you obtain ethics expertise?
☐ In-house ethicists
☐ Permanent external ethics expertise
☐ Ad-hoc hiring of ethics consultants (per project)
☐ Other (please specify): ……………………………
☐ Not applicable

D. Factors influencing the incorporation of ethical issues in HTA
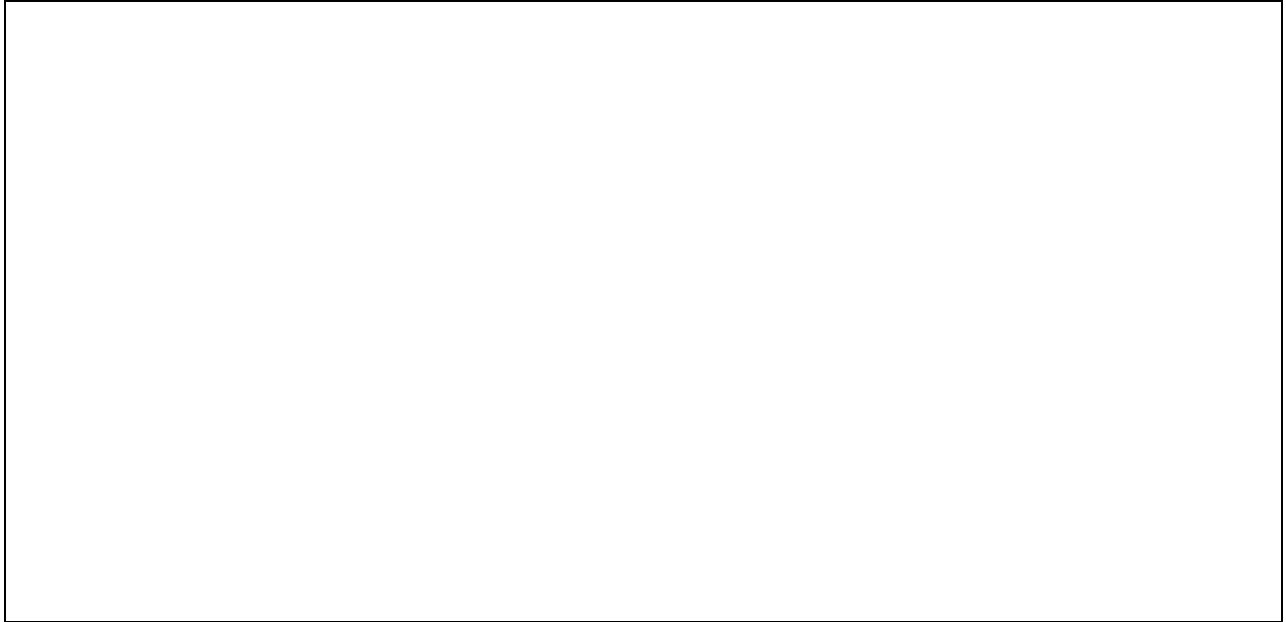
D1. What are the main barriers to incorporating ethical issues in HTA? (please select the most prominent barriers in your organization)
☐ Organizational policies and rules
☐ Limited organizational resources (human, financial, etc.)
☐ Negative attitudes of researchers involved in HTA
☐ Limited expertise of researchers involved in HTA
☐ Project timelines
☐ Lack/complexity of existing guidance documents
☐ Scarcity of ethical evidence
☐ Other (please specify): ……………………………
☐ No opinion

D2. What would encourage or assist HTA-producers in incorporating ethical issues into HTA?
☐ Enhancement of existing guidelines and frameworks
☐ Engagement of stakeholders in HTA process
☐ Holding training sessions and workshops for HTA-producers
☐ Engagement of ethicists in HTA procedures
☐ Demand by policy-makers
☐ Public pressure
☐ Other (please specify): ……………………………
☐ No opinion

Please use the space provided below to comment on any related issue not covered in this questionnaire:

Thank you for your contribution.

Supplementary Material 3- Characteristics of respondent agencies (n=26)

	n (%)
Type of agency	
Governmental or quasi-governmental agency	15 (57.7)
Governmental department	5 (19.3)
Research/ academic institution	4 (15.4)
Non-governmental special health board	1 (3.8)
Hospital HTA unit	1 (3.8)
Respondents position	
Researcher (scientist/methodologist/health economist)	12 (42.6)
Director of HTA unit/ agency	11 (42.3)
Program/ project manager	3 (11.5)
Types of technologies*	
Medical devices	26 (100.0)
Medical procedures	24 (92.3)
Public health interventions	18 (69.2)
Pharmaceuticals	15 (57.7)
Health system interventions	15 (57.7)
Screening tests and screening programs	1 (0.04)
Traditional & Complementary Medicine	1 (3.8)
Other prescribed care services	1 (3.8)
Types of appraisals*	
HTA Reports	23 (88.5)
Rapid Assessments	21 (80.8)
Systematic Reviews	14 (53.8)
Horizon Scanning	8 (30.8)
Technical Queries	7 (26.9)
Summaries Of Other HTA Agencies' Reports	2 (7.7)
Mini HTAs	1 (3.8)
Economic Evaluations	1 (3.8)
Policy Briefs	1 (3.8)
Other: *methodological/ informational/other HTA-funded research papers, commentaries*	4 (15.4)
Median number of appraisals performed by the agency per year	Median (range)
HTA report	5 (0-40)
rapid assessment	5 (0-200)
systematic reviews	1 (0-45)
technical queries	0 (0-15)
horizon scanning	0 (0- 25)
other	0 (0- 60)

*More than one option could be chosen

CHAPTER 4

Steps toward improving ethical evaluation in health technology assessment: a proposed framework

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Abstract

Background: While evaluation of ethical aspects in health technology assessment (HTA) has gained much attention during the past years, the integration of ethics in HTA practice still presents many challenges. In response to the increasing demand for expansion of health technology assessment (HTA) methodology to include ethical issues more systematically, this article reports on a multi-stage study that aimed at construction of a framework for improving the interaction between HTA and ethics.

Methods: The framework was developed through the following phases: 1) a systematic review and content analysis of guidance documents for ethics in HTA; 2) identification of factors influencing the integration of ethical considerations in HTA; 3) preparation of an action-oriented framework based on the key elements of the existing guidance documents and identified barriers to and facilitators of their implementation; and 4) expert consultation and revision of the framework.

Results: The proposed framework consists of three main components: an algorithmic flowchart, which exhibits the different steps of an ethical evaluation throughout the HTA process, including: defining the objectives and scope of the evaluation, stakeholder analysis, assessing organizational capacity, framing ethical evaluation questions, ethical analysis, deliberation, and knowledge translation; a stepwise guide, which focuses on the task objectives and potential questions that are required to be addressed at each step; and a list of some commonly recommended or used tools to help facilitate the evaluation process.

Conclusions: The proposed framework can be used to support and promote good practice in integration of ethics into HTA. However, further validation of the framework through case studies and expert consultation is required to establish its utility for HTA practice.

Introduction

There has been an increasing awareness of the need to incorporate ethics into the health technology assessment (HTA) process. This need is a consequence of the recognition that addressing moral and ethical issues can increase transparency and accountability of the HTA process and lead to better informed healthcare decisions (1). As a result, HTA producers and decision-makers are increasingly more interested in considering contextual normative issues and value judgments, in addition to the results of clinical and economic evaluations in HTA.

Despite its importance, integration of ethical aspects into HTA remains challenging for several reasons. One of the key challenges is the plurality of ethical methods that need to be understood by HTA professionals in order to be applied appropriately (2;3). Our systematic review of existing guidance documents for ethical analysis in HTA suggested that methods proposed to address ethical issues differ considerably in terms of philosophical approach, structure, and comprehensiveness, and that there is no "one right way" to evaluate ethical considerations around healthcare technologies (4). Another challenge is that HTA agencies too often fail to adopt the existing ethical guidance documents because most of the guidelines tend towards complexity and call for expertise, time and other resources that might not exist in their organizations. A recent survey of international HTA agencies revealed that only in 15% of the participating agencies, ethical evaluations were typically performed by individual, mainly external, ethicists or multi-disciplinary teams including ethicists. The majority of the surveyed HTA organization relied on non-ethicist HTA professionals to conduct ethical evaluations, when required (2).

We believe if HTA professionals are expected to take part in ethical evaluations, they need a systematic approach that places greater emphasis on the process and steps needed for identifying and analyzing ethical considerations around candidate healthcare technologies, rather than merely providing theoretical methods for ethical reflection. This systematic approach should help HTA practitioners better understand the ethical evaluation process, use relevant ethical evaluation tools and seek appropriate expert guidance in answering ethical questions, if needed.

A number of existing guidance documents come closest to fulfilling this need. However, they rarely focus on the operationalization of their proposed approaches. For example, the ethical evaluation component of the European network for HTA (EUnetHTA)'s Core model (5), is a comprehensive document that provides a checklist of questions covering ethical issues related to the technology and the HTA process, describes commonly used methods to answer the questions, and proposes a standardized reporting structure. Likewise, the guidelines developed by a number of European HTA agencies, including the Austrian (6), Danish (7), French (8), German (9), Norwegian (10), Spanish (11), and Swedish (12) agencies, promote similar systematic approaches to integrating ethical evaluation into the HTA process. However, all of these guidance documents provide few details on what is needed to be done in order to implement the proposed methodology in a routine HTA environment. A further step has more recently been taken by the Swedish Council on HTA to provide a framework that takes into account not only the nature of the HTA process, but also organizational, financial and regulatory elements, as well as the availability of ethical expertise (13). This framework that focuses on the identification and prioritization of ethical considerations in HTA provides only a brief description for operationalizing the ethics review process.

For HTA researchers with limited experience of performing ethical evaluations, there is still a need for a procedural guidance which would enhance their understanding of how an ethical evaluation can take place during a HTA process and to aid them in incorporating ethical evaluation steps into a typical HTA plan. The aim of this paper is to fill this gap by offering a structured action-oriented framework and a list of literature-driven supporting tools. It should be noted that we do not intend to "reinvent the wheel" by proposing an alternative approach to substitute existing ethical evaluation methods. Rather, our study is intended to provide a process-based framework that encompasses a range of evaluative actions provided by other ethical guidelines for HTA in order to illustrate and describe the steps that are expected to be taken by a HTA team in evaluation of ethical considerations. We believe such a framework would allow HTA producers not only to understand the ethics review process and make use of ethics in their assessments, but also to identify interconnections and overlaps between ethics and other domains of HTA. Our framework also brings together the procedural steps and potentially helpful tools to provide more flexibility to the ethical evaluation process in HTA and increase its applicability.

The remainder of this paper is organized as follows: we begin with a description of our multiphase research methodology. Then, we introduce our stepwise model and explain some important considerations which should be taken into account at each particular step. Next, we introduce a number of the most commonly used tools in ethical evaluation. Finally we offer further discussion of our proposed model and draw conclusions.

Methods

We initially performed a systematic review of the literature, published up to October 2013, with the purpose of identifying and mapping existing frameworks for ethics in HTA and methodological guidelines from national and international HTA agencies. The review identified 21 methodological articles and 22 HTA guidelines of varying complexity and scope. Data was abstracted, through content analysis, on methodological features of the identified guidance documents, particularly their areas of focus, theoretical foundation, analytical approaches, supporting tools, and required expertise. More details about this phase of research have been published elsewhere (4).

Then, to identify factors that are likely to influence the ethics review process, we conducted a comprehensive search in the literature to create a list of main barriers and facilitators of ethical evaluation in HTA. In addition, we performed a survey of the main HTA producing agencies throughout the world to learn about their experiences, methodological preferences, and their perceptions of the key barriers and enablers to incorporation of ethics in HTA. Ethics approval for the survey was granted by the Hamilton Integrated Research Ethics Board at McMaster University (REB 13-103). Informed consent was obtained using a recruitment email which described the aims of the study and notified participants that completion of the survey implied consent to participate in the survey. Therefore, a separate informed consent form was not required. The findings of the literature review and the survey are published in detail elsewhere (2).

The next stage was to draft a framework based on operational features of the identified guidance

documents, as well as practical barriers to avoid and enablers to encourage in performing an

ethical evaluation. We used data from the guidance documents included in our systematic review

(4) to generate a comprehensive list of main elements and sub-elements that needed to be

considered in an ethical evaluation and identify the common elements. The following a priori

categories were utilized to group action items: scoping, data collection, analysis, and knowledge

translation. However, as the analysis progressed, some preliminary categories were combined

and further categories were added. The identified barriers and facilitators were used to help

further define action categories and task items (2). The process was continued until seven final

action categories were established: 1) defining the objectives and scope of the evaluation, 2)

identifying stakeholders, 3) assessing organizational capacity, 4) framing ethical evaluation

questions, 5) ethical analysis, 6) deliberation, and 7) knowledge exchange or translation.

We generated a separate list of tools, identified in our systematic review (4), to help facilitate

addressing ethical issues in HTA and examined all in relation to their application and

appropriateness for each procedural step. Additional ethical tools were identified through

targeted searches in the literature and consultation with subject matter experts. Finally, a

summary table consisting of a brief description of the identified tools as well as some of the

strengths and weaknesses of each tool was generated.

Results

Our proposed framework consists of three key components: an algorithmic flowchart that

illustrates a set of steps for operationalizing ethical evaluation throughout various stages of the

HTA process; a stepwise guide, which breaks down each step into individual task objectives and suggests some questions that need to be addressed at each step in order to complete the suggested tasks; and a list of some commonly recommended or used tools, along with a brief description of their strengths and weaknesses. The Framework components are summarized below.

The algorithmic flowchart

As illustrated in Figure 1, our stepwise flowchart organizes the actions required for an ethical evaluation practice into seven main steps and four conditional steps that allow for revisions and improvements within and across the main steps of the evaluation process. Although in this figure, progression from one step to another is shown to be linear, it is important to note that in real practice ethical evaluation activities can often occur simultaneously or iteratively.

The stepwise guide

To make the framework useful for HTA practitioners, we have attempted to operationalize it into a guide, which can be seen in Table 1. The guide includes a non-exhaustive list of tasks and related questions which are drawn from our systematic review of ethical guidelines for HTA (4), input from experts in the fields of HTA and ethics (n=6), and from our study of barriers and facilitators of ethical evaluation in HTA (2). As with many ethics frameworks in other contexts, this guide is intended to aid HTA practitioners in identifying key considerations that should not be overlooked, while also helping them to think about possible action items.

Step1. Defining the objectives and scope of the evaluation

Before starting an ethical assessment, it should be ensured that the objectives of both the overall HTA, to which the ethical evaluation will be incorporated, and the ethical evaluation itself are set. In doing so, the role of ethics should not be over- or under-estimated. Rather, the scope and aims of ethical evaluation should be proportional to the candidate technology and the context (14). Clear objectives are important because the methods chosen for the collection and analysis of data will depend on the purpose of the assessment. Then, as with any other evaluation process, ethical assessment should begin with an exploratory phase to identify the existing knowledge base surrounding the technology of interest such as technological aspects, modes of application, range of possible clinical indications, safety issues, as well as the therapeutic, economic and organizational impacts of the technology.

Step2. Stakeholder analysis

Given the importance of stakeholder interests and values in an ethical evaluation and their influences over potential decisions, it is good practice to conduct a stakeholder analysis during the defining and scoping phase to make sure that values and preferences of potential stakeholders are effectively included in the ethical analysis. Nonetheless, stakeholder analysis can be undertaken throughout all steps of ethical evaluation.

During the scoping phase, potential stakeholders can be identified through brainstorming, collecting and analyzing quantitative or qualitative information, and asking identified stakeholders who they would suggest as relevant stakeholders for the technology of interest. A typical stakeholder analysis involves assessing the interests of the identified key stakeholders,

such as patients, healthcare providers, decision makers, family members and the general public in the candidate technology; assessing their importance and level of influence over the HTA process and decision-making; determining who stands to benefit and who stands to lose if the candidate technology is introduced, in what ways and to which extent; and identifying the most appropriate ways to engage stakeholders (15;16). Some useful tools for stakeholder analysis are introduced in Table 2.

Step3. Assessing organizational capacity

The following resources are necessary in performing an ethical evaluation: a person with a strong educational background and experience in applied ethical theory, sufficient financial resources and time for conducting the evaluation, and the capacity for training, if needed. Therefore, it is important to assess the level of organizational readiness along each of these dimensions in order to balance available resources with the requirements of ethical evaluation.

It must be ensured that sufficient knowledge, experience, and skills exist in the organization to collect ethics-related data and to perform a comprehensive ethical analysis for several reasons. Firstly, since ethical evaluation is an approach which deals with norms and values, conducting such an evaluation would not be possible without a reasonable amount of knowledge of ethical theories and principles. Secondly, because the scope of ethics literature is wide and can include theory as well as both quantitative and qualitative study results, HTA practitioners involved in ethical evaluations should be able to effectively appraise ethics literature and reflect on the collected information. Thirdly, a well-performed ethical analysis uses moral reasoning rather than merely describing facts and values. Hence, the rigour of ethical reasoning is usually

dependent on how skillfully the analysis has been performed. Furthermore, the capacity in methodologies associated with ethical analysis through public discourse is often lacking in some HTA organizations (17). Therefore, to get involved in public participatory processes, HTA professionals might need to acquire a range of new skills in different methods of public engagement before getting involved in such research activities (14;18).

Step4. Framing ethical evaluation questions

Recognition of existing ethical dilemmas or the ones that are perceived likely to emerge after implementation of the technology (hypothetical dilemmas) is essential for the formulation of ethical questions that need to be answered. Identification of the existing ethical issues that could be resolved through the introduction of the technology should also be accounted for. Zydziunate *et al.* (19) systematically reviewed ethical dilemmas that might affect decision-making within health care systems and suggested that ethical dilemmas in healthcare might happen in institutional, local or national levels. The review listed the following terms that had been commonly used in defining or discussing ethical dilemmas: "continuing balancing" between health care needs and budgets, "result of resource allocation", "gap between professional obligations and possibilities", "ethically controversial situation", "concern about interactions", "outcome of medical choices", "concern about society's access to healthcare resources", and "ethically difficult or ethically challenging situation".

In practice, it might not always be necessary to make a comprehensive list of existing ethical conflicts or controversial issues through a systematic inquiry. However, it is important to discuss and specify which of the recognized ethical dilemmas and arguments are more relevant to the

assessment and provide a justification for why these could be relevant. One familiar example is the dilemma that might arise in situations involving genetic testing technologies. Genetic test results, by nature, can reveal aspects of the tested individual's susceptibility to health problems (potential for stigmatization or discrimination). In addition, they may have implications on the blood relatives of the tested individual, who might also request to know their family member's genetic test results (potential for information abuse or intrusion of privacy). These aspects of the technology should be explored and discussed while framing the ethical evaluation questions. At this phase of evaluation, a priority should be assigned to ethical questions that may have greater implications on decision making. However, the HTA team must allow flexibility for adding questions during the ethical evaluation process. Overall, this step might be affected by the evaluators' philosophical orientation, background knowledge, and experience.

Step5. Ethical analysis

As it was mentioned before, the present framework does not aim to provide instructions on how to perform an ethical analysis but rather assumes that HTA team members who are responsible for the analysis of ethics data have the knowledge and skills to take on this important task. Ethics expertise can be critical at this step, depending on the type of the assessment. A normative (principle- or theory-based) evaluation should generally be performed with the help of experts with knowledge in ethical theory. In participatory or interactive assessments, where expert and lay opinions are considered equally valuable, ethicists can play an active role by providing rationale for potentially useful analytical approaches, scientific and theoretical inputs to stakeholder and public debates and assisting stakeholders in reaching a consensus (14). In sensitive topics, it may be desirable to seek discussion from more than one ethicist. Other HTA

practitioners (non-ethicists) can also have a role, although necessarily limited, in ethics review and analysis (e.g., helping with formulating ethical questions and searching for potential solution through systematically identifying and summarizing ethics-related data, helping with participatory research, etc.). The following practical recommendations are suggested for performing an ethical analysis in HTA:

In order to get a deeper understanding of ethical dilemmas surrounding a particular healthcare technology, it is essential that the information gained during the previous steps be reviewed carefully to examine data for adequacy and usefulness (20;21). Systematic reviews of the ethics literature should draw on findings from both normative and empirical literature. The objective of the study selection process for an ethical evaluation should move beyond merely selecting articles containing information on pre-identified ethical issues and opinion pieces to well-founded and carefully reasoned arguments and analyses. Depending on the aims and methodology of the evaluation, a range of primary data collection methods can also be employed to gather additional data at this step, some of which include: surveys, observations, analyses of texts and documents, stakeholder interviews, focus group discussions, Delphi panels, and consensus conferences. Data from different sources need to be collected in order to avoid uncertainty. In addition, due to the iterative nature of data collection to analysis process, selection of data sources and data collection methods should remain flexible throughout the ethical evaluation. For example, stakeholders or informants who are able to provide additional facts, and verify or correct uncertain information might be selected on the basis of the preliminary analysis, or new techniques might be employed to gather required information. The collected data should be carefully assessed regarding its reliability and credibility before ethical

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reasoning takes place. This can be achieved by ensuring that the facts and values are collected in a systematic way; the concepts and arguments are articulated clearly, coherently and consistently; and the clinical, social and policy implications of the arguments are made clear (21-23).

Ethical reasoning is the process of examining ethical dilemmas through evaluation of various types of information and applying guidance from moral norms, principles, or theories. Ethical reasoning can be accomplished through normative reflection or value-based descriptive approaches which mainly employ public involvement methods. However, it can be useful to employ more than one method in a given evaluation to: help attend to the problem of bias, address the complexity of ethical dilemmas and uncertainties around healthcare technologies, and better justify HTA decisions (14;24-27). Different approaches can be compared and contrasted to more thorough and balanced results.

Several ethical theories can be used to guide an ethical analysis process. Utilitarianism and deontology are the two most commonly referenced perspectives in moral philosophy. From the utilitarian perspective, the ethical action or decision is the one that will produce the best outcomes, usually measured as the greatest benefit for the greatest number of people; whereas, the deontological perspective focuses on duties, rules and obligations to respect the interests of individuals (28). Examples of other ethical theories that have been commonly used are egalitarian perspective which focuses on fairness and justice, and virtue ethics which views the moral character and virtues of individuals as the central point of rightness or wrongness of actions, and emphasizes contextual factors (28). It is important to note that the results of theory-

based analyses may be influenced by the analysts' knowledge, their experiences, values, and attitudes, as well as the technological, organizational, social, and political contexts in which the analyses are performed. Ethical analyses are also at risk of bias due to actual or potential conflict of interests in the HTA organization, such as which may influence the ways in which ethical information is collected, analyzed and interpreted. Therefore, it is good practice to provide a sound justification of the choice of the methods and disclose any financial and non-financial relationships with organizations or groups who may have an interest in the candidate technology and its implementation.

Step6. Deliberation

Once the preliminary analysis of ethical data is completed, it is desirable to discuss the results with the members of the multidisciplinary HTA team, and other experts if needed, in order to verify plausibility and reasonableness of the results. To ensure that the results are perceived as relevant by stakeholders and the public, it is also important to use public engagement methods to take in a variety of inputs from the groups whose values and preferences can provide a means for a better informed and legitimate policy decisions (29). Although engagement of the public (including relevant stakeholders) in an ethical evaluation process, and in HTA in general, has been promoted at different levels, the common exercise is to gather the public input in an ad-hoc basis through deliberative methods such as surveys, focus group discussions, etc. Alternatively, the public input can be sought directly from the public representatives who are involved throughout the HTA process, or through an institutionalized approach, where the public or specific stakeholder groups are asked, as consultants, to provide input for decision-making in an ongoing basis (29). Despite its importance, as a democratic exercise in ethical evaluation, public

involvement methods can be challenging to perform due to their complexity, costliness, and time consuming nature (30).

Additional expert insight might be necessary to ensure the plausibility of the produced results during stakeholder hearings, before a particular conclusion is reached and the final report on ethical issues around the technology is written.

Step7. Knowledge exchange/translation

The purpose of HTA is primarily to support healthcare policy-makers in making evidence-informed decisions, and secondarily to help advance knowledge about a particular health technology and stimulate further research (31). Therefore, the dissemination of the HTA findings, including ethical aspects, must be timely and appropriately tailored to the needs of potential users.

In order for the results of an ethical assessment to be utilized as an input for decision-making, the knowledge translation activities should begin in the earliest stages of the HTA process, through an effective interaction between HTA-producers and decision-makers, and continue throughout the evaluation (32). The results need to be communicated in a manner that can be understood and easily utilized by decision-makers. The feedback from potential users should be received throughout the project and used to improve the quality of the research. HTA reports should address various dimensions of an existing or hypothetical ethical problem surrounding the technology of interest, using all relevant evidence from research and non-research sources, and

applying suitable analytical approaches. It is also important to address how different stakeholders

and members of society might be affected by the implementation of the technology or otherwise.

HTA findings can also be disseminated among other relevant target groups, such as healthcare

researchers, clinicians, healthcare service providers (e.g. hospitals), third party payers,

biomedical manufacturers, patients, and the general public. However, it is essential to translate

the findings (including the results of the ethical analysis) into formats that are understandable

and useful to the above-mentioned groups of audience (7).

Selected tools

Table 2 provides a list of tools and techniques to support ethical evaluation tasks. This list does

not include every possible tool that could potentially be used at each step of the proposed model,

but has explored some of the more common ones that can assist HTA practitioners in evaluation

of ethical considerations. It is important that HTA practitioners with responsibility for

addressing ethical issues have a comprehensive knowledge and understanding of such tools in

order to choose tools which are appropriate for varied types of ethical objectives and evaluation

tasks.

Four categories of tools can be distinguished in Table 2: ethics literature review and appraisal,

stakeholder analysis, exploring stakeholder values and preferences, and identification and

analysis of ethical issues. We also searched for computerized support tools for aiding ethical

analysis and identified a number of tools which were designed to help the users in summarizing

and structuring ethical arguments, describing potential inter-relations between the interests of

different stakeholders, or analyzing the impact of alternative technologies on various

stakeholders' interests. In our toolbox, we only included the computer programs, such as

EthXpert (33) and Ethos (34), that had originally been created as ethical decision-making support

tools. Although none of these computer programs had been tested and validated for use in HTA,

they could potentially be applicable in ethical analysis for HTA.

Discussion

In this article we offer a stepwise framework for the evaluation of ethical considerations

throughout the HTA process. It includes a set of procedural steps, examples of questions to be

answered at each step, and a number of supporting tools to facilitate ethical evaluation. This

framework is intended to guide HTA producers, especially those who are not accustomed to

performing ethical analyses, and to provide them with a knowledge base necessary for dealing

with ethical issues in HTA. It may also be used by researchers, evaluators, or decision-makers in

order to critically appraise the evaluation process used for an ethical analysis. Our framework

can also be used for educational purposes, especially to show the flow of activities needed for a

successful evaluation of ethical issues.

We believe that only by fully understanding all of the different steps of ethical evaluation, and

specific issues that may arise at each step, can HTA teams integrate ethics in their assessments.

While there is no lack of guidelines and tools for assessment of ethical issues in HTA (4;35), the

core idea of our article is to propose a procedural framework for integrating ethical evaluation

into the actual ongoing process of HTA from designing to project implementation and

knowledge translation. Our framework was developed through a rigorous process that involved

systematic reviews of literature, content analysis of existing guidance documents, an exploratory survey to understand the factors contributing to an effective ethical evaluation in HTA organizations around the world, and expert opinion. The framework has a number of distinctive features that make it different from previously proposed frameworks for ethics in HTA:

- The systematic nature of the framework promotes a better understanding, among HTA practitioners, about a comprehensive ethics review and sensitizes them to the importance of ethical considerations in their assessments;

- The process break-down structure of the framework can reduce the complexity of ethical evaluation by mapping and illustrating required activities and, hence, reduce the risk of neglecting important methodological steps.

- The guiding questions associated with each group of activities can help HTA teams in thinking about potential questions to answer at each step, and thus facilitate a more comprehensive evaluation.

- The suggested tools can provide support at different steps of developing and integrating an ethical evaluation.

- The framework gives the users flexibility to selectively add or remove activities, tasks and tools, or tailor the way particular steps should be taken, based on the needs of their organizations;

- Allows for accountability and quality assurance by enabling managers and evaluators to check if relevant methodological steps have been completed; and

- Serves as a basis for development of training material for HTA professionals.

In summary, the strengths of our proposed framework lie in its structured yet flexible approach to the evaluation of ethical considerations in HTA. It can, therefore, be applied by HTA practitioners to the assessment of a wide range of healthcare technologies, using a variety of ethical inquiry methods.

In spite of its strengths, our proposed framework also has limitations. First, to use the framework HTA producers may require information, data and expertise and other resources that may not be readily available in a typical HTA organization. Qualitative evidence, stakeholder input and normative judgements are usually required to address ethics-related questions. Our framework fails to deeply address the ways in which ethical data should be tackled or specify how the evaluation process should be applied in different contexts. Second, the current version of our stepwise framework lacks an example case study where all the steps are applied. Furthermore, the validation of the proposed framework was not performed as part of this research project.

We will undertake further work to validate the framework and test its practicality through case studies, seeking stakeholder feedback, and expert opinion. Based on the results from the case studies and feedback received from the experts and potential users, we are planning to: (a) modify the stepwise framework by adding or removing steps; and (b) enhance its practicality by adding flow charts that illustrate details of various steps, and auxiliary tools or checklists to facilitate the ethical evaluation process; and (c) perform a final validation of the framework using further case studies.

Conclusion

Despite the increasing attention given to the incorporation of ethical considerations in assessment of healthcare technologies, HTA producers continue to face challenges in integrating ethics to HTA. The intention of this research project has been to construct a procedural framework that considers the nature and sequence of ethical evaluation process in the context of HTA. The proposed framework provides a conceptual foundation to allow for ethical issues to be addressed in HTA. Our framework can serve as a starting point towards a set of comprehensive strategic guidelines and the supporting instrumentation for integrating ethics in HTA. This framework can be used to support and promote good practice in integration of ethics into HTA. However, for a wider use and dissemination, its content needs to be applied in various HTA projects and validated through consultation with experts and policy makers.

List of abbreviations:

Health Technology Assessment (HTA); European Network for Health Technology Assessment (EUnetHTA)

Competing interests:

The authors have no conflict of interest to declare.

Authors' contributions

All co-authors on this publication contributed to the conception and design of the study. NA executed the systematic reviews of the literature, and led the survey of HTA organizations. NA carried data analysis. All authors contributed to the development of the framework. NA drafted

the manuscript. LS, DO and JET critically revised the article. All authors have read and approved the final manuscript.

Acknowledgements

Figure 1- Stepwise model for ethical evaluation in HTA

A. Planning | B. Evaluation | C. Dissemination

Communication with other aspects of HTA

Discuss with experts and decision-makers

Step 1
Define the objectives and scope of the evaluation

Is the scope of ethical evaluation clearly defined?

No

Yes

Step 2
Perform stakeholder analysis

Step 3
Assess organizational capacities

Is sufficient capacity available?

No

Yes

Identify sources of methodological and other support

Step 4
Frame ethical evaluation questions

Are the questions already addressed elsewhere?

No

Yes

Step 5
Perform ethical analysis

Step 6
Deliberate with experts and stakeholders

Review and revise data collection tools and /or analysis methods

No

Are the evaluation questions addressed?

Yes

Identify context-sensitive issues

No

Are the results transferable to the current context?

Yes

Step 7
Knowledge exchange/ translation

D. Decision-making

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Table 1- Stepwise guide for the ethical evaluation process in HTA

Steps	Evaluative tasks	Potential questions
1) *Defining the objectives and scope of the evaluation*	☐ Clarify the objectives and the scope of the HTA project	- What is the purpose of the HTA project (e.g., providing input for decision-making, formulating recommendations for practice guidelines, serving academic purposes)? - What is the rationale for the assessment of the technology (e.g., changing current practice, uncertainty/disagreement about benefits or risks of the technology)? - What are the information needs of potential users of the HTA findings?
	☐ Consider ethical issues around the HTA project itself	- Why is the assessment undertaken? Who has requested it? - Is there any special interest in the assessment or pressure from authorities, manufacturers, patient groups, etc.? - Is there any conflict-of-interest concerns?
	☐ Identify existing knowledge base about the technology	- Are there any characteristics of the technology that may raise ethical concerns (e.g., risk/benefit profile, utilization in vulnerable populations, access issues, modes of application) - What is the current practice? - What is the desirability of the technology (e.g., positive or negative utility values, QALYs) - What are the costs and organizational requirements for the implementation of the technology?
	☐ Specify the objectives of ethical evaluation	- What the HTA team/organization intends to achieve by performing and ethical analysis (e.g., a description of ethical issues around the technology, identifying and resolving uncertainties around implementation of the technology by learning about stakeholder values and societal interests or through philosophical reflection)?
2) *Identifying stakeholders*	☐ Identify potential stakeholders; engage key stakeholders to identify other stakeholders	- Who (potential groups or individuals) might affect or be affected (benefit/ loose) by the introduction of the technology (e.g., decision-makers, manufacturers, healthcare providers, societal actors, patients and their families)?
	☐ Identify the ways in which the above groups may be affected by the implementation of the technology	- What are the potential consequences of implementing the technology on disadvantage groups (access, equity, etc.)? - What are the potential consequences of implementing the technology on other stakeholders?
	☐ Identify the ways in which the above groups may affect the implementation of the technology	- What are the known interests of stakeholders in the implementation of technology? - What opportunities (level of power) do stakeholders have to get involved in making decision about the implementation of the technology?

Steps	Evaluative tasks	Potential questions
3) Assessing organizational Capacity	☐ Define key requirements	- What are the policy directions and priorities of the HTA organization and how might these influence evaluation of ethical considerations? - Is there a shared understanding of objectives and outcomes of HTA and ethical evaluation? - Are the opinion leaders in the organization supportive of integrating ethics in HTA? - Do the project timelines allow enough time for the completion of an ethical evaluation? - Are there any feasibility issues regarding ethicist involvement or stakeholder engagement? - Does the organization have any previous experience with ethical evaluations?
	☐ Establish a team consisting of ethical expertise, HTA practitioners with experience in evaluation of normative aspects of healthcare technologies, and relevant stakeholders (when needed)	- Is the ethical expertise available in house? If not, are any external ethicists available to be recruited for the purpose of this evaluation? - Are there sufficient staff members with required characteristics (knowledge, skills and attitude) available to take part in the ethical evaluation?
4) Framing ethical evaluation questions	☐ Recognize potentially relevant ethical problems and solutions that may arise from the introduction of the technology	- Is there any potential conflict between the technology and basic human rights, social and cultural values, patient's autonomy, etc.? - What are the moral characteristics of the technology (e.g., risk/benefit profile, health improvement at the individual and society levels)? - Does implementation the technology require any life style modifications? - What are the long term effects of the technology on the users, their family members, and society (e.g. psychological impact, discrimination)?
	☐ Map the current practice from an ethical perspective	- What are the key problems with the current use of technology (e.g., costs, equity problems, privacy, misuse of technology, freedom)? - What are the affected groups' perceptions about the current practice?
	☐ Identify sets of governance steps that might be necessary to resolve potentially relevant issues	- What solutions have been proposed to deal with the identified ethical problems? - How effective these solutions have been reported to be?
	☐ List ethical issues around the technology	- Have I been able to identify any ethical issues around the technology (e.g., outcomes of medical choices, society's access to the technology, ethically controversial situations at political or local levels, and ethically challenging situations at societal or healthcare system levels)?
	☐ Justify what issues should be included in the ethical analysis, and why	- Which of the identified ethical issues are more relevant to the HTA project's goal, and why? - Which of the identified ethical issues are more important, and why?
	☐ Use dialogues and/or other deliberative methods for input seeking from ethical and technical experts as well as potential users, if necessary	- Has the plausibility of the identified ethical issues been stablished or discussed? - What insights are available from experts or stakeholders to aid in finalizing ethical evaluation questions?

Steps	Evaluative tasks	Potential questions
5) ***Ethical analysis***	☐ Choose an appropriate methodology to address identified ethical dilemmas	- What methodologies are described in the literature or have been employed by others to study similar problems? - What theoretical paradigm is chosen by the research team to inform the ethical evaluation (utilitarian theory, deontological ethics, virtue ethics, etc.)? - What is the most practical and reliable approach to collect and analyze ethical data, considering the purpose of analysis, available expertise and other resources and feasibility of stakeholder engagement (e.g., empirical approach [using quantitative data], philosophical approach [using ethical theories and principles], narrative approach [using facts, value judgments, and stakeholder preferences], or a mixed approach)?
	☐ Justify the choice of method	- What theoretical paradigm best fits the evaluation questions? And Why" - How the selected approach might be helpful in answering evaluation questions?
	☐ Review existing information and acquire additional relevant information through: — An extensive search in quantitative and qualitative literature — Deliberative methods	- Have adequate data been collected to serve the purpose of the ethical analysis? - What information is available in the literature about ethical, social or legal impact of the technology? - Is there any (retrospective, current or futuristic) information available on the use of the technology in different social and cultural contexts? - What arguments are available in the literature in favour of or against the technology? - What are the stakeholders' values and preferences? - What controversies and potential conflicts exist at the local, societal and political levels around implementation of the technology?
	☐ Ensure data from all sources are considered for analysis	- Has data from all possible sources collected for the ethical analysis (e.g., quantitative and qualitative evidence, stakeholder hearings, and expert opinion)? - Is triangulation of data sources possible?
	☐ Examine the collected data for logic and coherence, validity and reliability	- What is the level of internal consistency of data? Is the collected data reliable? - Is there any self-contradiction or incoherence in the collected data? Does a fundamental logic exist among the collected facts and values? - What are the e factors that could influence generalizability of the evaluation results?
	☐ Synthesize and integrate collected data (facts and values) into ethical arguments — -Apply the principles of biomedical ethics — -Perform philosophical arguments on the ethical questions from the perspective of ethical theories — -Reflect on possible solutions	- Does the implementation or use of the technology challenge the basic principles of biomedical (e.g., beneficence, non-maleficence, autonomy, justice, vulnerability,) - What are the key arguments in favour of using the technology? - What are the key arguments against implementation of the technology? - Are clinical or economic benefits of the technology justifiable from the chosen (various) ethical perspective(s)? - Are the arguments sound and clear? - What are the possible options for acting, and their consequences?
	☐ Acknowledge your own values and philosophical interest	- What is your position (perspective) on the matter? - How would you interpret the data, if you were in the stakeholders'/policy-makers' shoes? - How confident are you that your position will remain the same in the matter over time?

Steps	Evaluative tasks	Potential questions
6) *Deliberation*	☐ Discuss the results of evaluation with an expert group to assess their relevance and completeness	- What do the experts have to say about the relevance of the collected data? - Do the experts have any suggestions as to what other sources of relevant information are available?
	☐ Choose an appropriate method to discuss the results of ethical analysis with relevant stakeholders to seek their feedback on the results	- Who are the appropriate stakeholders to take part in or provide feedback on the analysis? - What are alternative sources of values for interpreting ethical analysis findings? - What are the ways that encourage identified stakeholders to provide required information. - What are the main concerns, preference, and emergent needs of stakeholders? - To what extend the stakeholder engagement activities have captured required information?
	☐ Seek additional expert insight, if necessary, to ensure about the plausibility of the produced results during stakeholder hearings.	- Is it required/ worth to engage a group of experts in a discussion of the ethical evaluation results? - Do you have any specific questions/ uncertainties which you would like the experts to address?
7) *Knowledge exchange/ translation*	☐ Refine your target audience that might be interested or may benefit from the results of HTA	- Who is the target audience (e.g., policymakers, healthcare providers, patient groups, academic audience)?
	☐ Refine information needs of your target audience	- What are the ways in which the report will be used (e.g., direct use of knowledge for problem-solving, conceptual use of knowledge for perception-shifting or understanding, political use of knowledge for supporting or challenging policy decisions)?
	☐ Structure a presentation format to address the information needs of target audience	- How should the evaluation results be made available to users (in terms of content and format)?
	☐ Report the results of ethical analysis in a transparent and effective manner	- Are the criteria and logic for the choice of methodology and selection of stakeholders disclosed? - Are the identified gaps in the literature, concerning ethical issues and values, addressed? - Are all favorable and non-favorable arguments reported? - Are anticipated changes that may follow from the implementation of the technology discussed? - Are the findings summarized and the most important value issues highlighted?
	☐ Integrate knowledge translation in all steps of the assessment	- Has there been an integrated flow of information among team members working on different aspects of the technology (clinical, economic, ethical, social, legal, and organizational aspects) throughout the HTA process?

Table 2- Commonly used tools for ethical evaluation in HTA

Tool	Description	Strengths	Challenges	References
A. Ethics literature review and appraisal				
Methodologies for the search and retrieval of information on ethical issues in HTA	Methodological approaches for the systematic retrieval of ethical information are discussed in two articles. These articles provide recommendations for good practice in selection of sources of ethical information, designing and executing ethics-specific search strategies, quality check of search results, and reporting information retrieval process.	Encourages a separate literature search relevant to ethical questions, using the common retrieval framework for effectiveness assessments.	The proposed search terms or strategies might not be sufficient for retrieval of all relevant ethical issues. Additional targeted searches might be necessary.	(36;37)
Tools for critical appraisal of empirical ethics research	An article by Strech discusses the appropriate criteria for appraisal of empirical research required for ethical reasoning. He suggests four appraisal criteria related to the relevance of study questions, selected outcomes and measure, study design and generalizability of study results.	Addresses some important challenges of considering empirical data in ethical analysis.	No detailed guidelines or case studies are provided for how to apply the appraisal criteria.	(38)
	Mertz et al propose a set of structured quality criteria which can be used as a checklist to guide empirical ethics researchers and appraisers in the following four domains: research methodology, scientific and social relevance of the research project, interdisciplinary research practice, and research ethics.	Designed based on an in-depth analysis of existing empirical ethics research and the opinion and experience of experts in the field of medical ethics.	The practicality of the criteria is not tested in real life empirical ethics research practice.	(20)
A tool for critical appraisal of normative medical ethics literature	McCullough et al offer a tool to help clinicians (particularly obstetrician/gynecologists) in critical appraisal of normative bioethics literature. The tool incudes four questions about the focus of the study, validity and soundness of the study results, as well as their implication and usefulness in clinical practice.	Designed based on the standards of critical appraisal of argument-based ethics and evidence-based medicine.	Judgment about the validity and quality of ethical analyses and arguments requires some level of knowledge about ethical reasoning. This might not be an easy task for the target audience of the tool, i.e., physicians.	(21)
Guidelines for systematic reviews of ethical evidence	Strech e t al propose a 7-step approach for systematic reviews of empirical bioethics literature, The stepwise process involves definition of review questions, development and execution of search strategies, assessment of relevance and quality of identified studies, and analysis and presentation of data.	Practical recommendations are provided for each step. The application of the proposed approach is illustrated with an example.	The proposed search algorithms are not definitive and might need some modifications depending on the context and review questions. Data analysis and presentation may require some level of knowledge and skills in synthesis of qualitative data.	(22)

Tool	Description	Strengths	Challenges	References
	Strech and Sofaer also offer a methodology for systematic reviews of non-empirical reason-based bioethics literature. Their model provides instructions for formulation of review questions and study selection criteria, identifying eligible literature, data extraction and synthesis, as well as presentation of the review results.	Structured based on the common steps of a systematic review process. Provides a detailed description of operational steps, and examples of how to apply the model in practice.	Performing a "systematic" review based on this model might be time-consuming. This type of review requires some level of knowledge about ethical reasoning. be time-consuming and	(23)
B. Stakeholder analysis				
Stakeholder Power/ Interest grid	This tool is a four quadrant matrix that classifies stakeholders in relation to the power that they hold and their level of interest in the technology. Power classification can be based on the ability of stakeholders to define or influence health care systems and services, change the way services are provided, or guide the public opinion.	Highlights the importance of actors and interest groups in the technology	The stakeholders interests, perceptions positions, and influence are subject to change	(39)
Stakeholder SWOT	A SWOT analysis (Strengths, Weaknesses, Opportunities, and Threats) can help in understanding the interests of key stakeholders, the actions they can take to support and the risks that they pose to implementation of the technology.	Can be used to stimulate and organize thoughts and discussions in stakeholder analysis.	Procedures for performing a SWOT-analysis are not clearly defined. The analysis is prone to subjective biases of the assessors.	(40)
C. Public/ stakeholder engagement				
Exploring public values and preferences	A methodology document published by the National Coordination Centre for Health Technology Assessment (UK) presents the results of a systematic review of qualitative and quantitative approaches to involving the public in in HTA. The document identifies and describes details of the techniques that can be used to obtain public preferences and makes recommendations regarding the use of different techniques. Some of the commonly used methods identified in this document are as follows: –Quantitative techniques, including ranking (e.g., simple ranking, qualitative discriminant process, and conjoint analysis) rating (e.g., visual analogue scale) and choice-based (e.g., standard gamble, time-trade-off, discrete choice conjoint analysis and willingness to pay) methods. –Qualitative techniques, including individual interviews, focus group discussions, Delphi technique, citizen's juries, consensus panels, and nominal group techniques.	Summarizes and compares various techniques in a single document. Uses pre-defined sets of criteria to evaluate methodological issues of different techniques (e.g., validity, reliability/ reproducibility, generalizability, acceptability to respondents, or cost) identified methodologies. Provides examples of how the techniques have been used in research practice.	No single best technique or group of techniques for public engagement is recommended by this document. Users of the tool may require background knowledge and specific skills that enable them to choose and conduct an appropriate public engagement technique.	(41)

Tool	Description	Strengths	Challenges	References
D. Identification and analysis of ethical issues				
The Socratic approach (Hofmann's guiding questions)	This approach consists of 6 steps, whereof one step covers 7 main questions and 33 explanatory and guiding questions. This checklist is designed t for identification of and reflecting on ethical data throughout the HTA process, and for reflexive dialogue with stakeholders.	Takes into account several ethical perspectives and analytical approaches. Can be used by HTA practitioners who may be less familiar with ethical analysis. Facilitates ethical analysis.	Users of the tool may require some level of ethical knowledge in order to use appropriate approaches to answer the questions.	(42)
HTA core model's assessment element cards (AECs)	AECs describe the details of the information that is outlined by the basic units of the HTA Core Model (assessment elements). Each AEC provides information on the element, its importance and transferability for different applications (diagnostic, surgical, pharmaceutical or screening technologies), and appropriate sources of information and research methodologies to address the question defined by the element. The ethical domain of the Core Model includes 19 elements related to the 19 ethical issues on the topics of beneficence/non maleficence (4 AECs), autonomy (4 AECs), respect for persons (3 AECs), justice and equity (3 AECs), legislation (2 AECs), and ethical consequences of HTA (3 AECs).	Designed to provide structured information required for answering the generic question defined by each assessment element. Useful when producing HTA reports based on the HTA Core Model.	The way in which AECs should be used as a part of the assessment is not fully addressed in the model.	(5)
Ethical matrix	Ethical matrix is an analytical tool to aid ethical analysis of technological options The matrix uses a tabular format to identify ethical impact of a particular technology on different stakeholders. The table lists a set of prima facie moral principles, typically the four Beauchamp and Childress's moral principles (autonomy, beneficence, non-maleficence, and justice), along one axis and different stakeholder groups along the other axis. Relevant facts and values are usually listed in each cell of the ethical matrix. Ethical matrix can be used either to identify ethical considerations around the technology or to quantify and compare the impact of the technology on different principles using semi-quantitative scores (e.g., ranging from -2 to +2).	Facilitates ethical analysis by simplifying and structuring ethical discussion Raises awareness of a wide range of ethical concerns Helps researchers and decision-makers to avoid bias towards a specific moral principle. Can be used in both expert-led and participatory/deliberative ethical evaluation processes.	May become large, complex and difficult to manage, when too many moral principles are listed or diverse groups of stakeholders are identified.	(43)
Consequences table	A summary table of consequences of using and not using a particular healthcare technology is recommended in the HTA core model as an open framework for performing ethical analysis. This table summarizes key benefits and adverse impacts of implementing of the technology or	Allows for highlighting key impacts of a particular technology on various domains of HTA. Can be used by decision-makers to compare anticipated ethical issues	Cannot be used as a substitute for careful ethical reflection	(5)

Tool	Description	Strengths	Challenges	References
	otherwise on various stakeholder groups. A consequences table summarizing positive and negative impacts of the technology on all domains of HTA, along with references to the quality of their evidentiary sources, is also proposed as a part of the HTA core model's reporting template.	around alternative technologies in relation to other domains.		
E. Computerized support tools for aiding ethical analysis				
EthXpert	EthXpert is a computer program designed to help the user in summarizing and structuring ethical problems, describing potential inter-relations between the interests of different stakeholders, and analyzing the impact of alternative technologies on various stakeholders' interests.	Does not focus on a specific audience or any specific contexts. Therefore, can be applied to ethical evaluation in HTA.	In some cases, the use of the these computer programs can be difficult and time consuming, especially when one needs to include all details about complex ethical problems, or too many different perspectives.	(33)
ETHOS	Ethos is a computer program that provides a framework for organizing, storing and analyzing ethical information needed for problem solving or decision-making. The program allows for ethical analyses using different ethical theories and approaches.	Illustrates the flow of data collection and analysis in a map format. Enables the user to add or remove information through an iterative process.	The use of the software may require investment in resources.	(34)

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CHAPTER 5

Putting the Stepwise Ethical Evaluation Framework into Practice

Introduction

In the previous chapters, the results of a multiphase research work that led to the development of a stepwise framework for the evaluation of ethical considerations in health technology assessment (HTA) were reported. In this chapter, the framework is applied to the case of a genetic test for colorectal cancer (CRC) patients. It should be noted that this case study is illustrative and should be read in conjunction with the guidance provided in Chapter 4. Both chapters 4 and 5 are intended to be read by HTA team members (managers, researchers and policy-makers) who are less familiar with ethical evaluation methods, but may have a role to play in the process of ethical evaluation, if it becomes routine practice in HTA settings. Hence, this hypothetical case study is not intended to cover every possible aspect of an ethical evaluation, but rather to outline key tasks, strategies, and provide examples of process outputs that could be considered when attempting to perform an ethical evaluation in HTA.

This case study has been selected for a number of reasons. Firstly, the case of genetic testing for cancer patients corresponds to an area with several ethical concerns that should be explored in order to ensure effective decisions about the use of the technology. Secondly, due to the ethically sensitive nature of genetic tests, these issues are well addressed in the literature (e.g., privacy and confidentiality issues, and potential for discrimination). Thirdly, ethical considerations relating to genetic tests may have

substantial policy implications. In order to exemplify different issues that may arise in a real-world HTA setting, the research objectives for this case study have been taken from an ongoing HTA project that has been funded by the Canadian Agency for Drugs and Technologies in Health (CADTH)(1) in response to the increased demand for the test in the Canadian context. However, outputs of this CADTH project are not used in any of the examples provided in this chapter.

CASE STUDY

Genetic testing for patients with CRC

The condition: CRC is one of the most common malignancies, representing the third most common cancer in men and the second in women worldwide,(2) and the second leading cause of cancer deaths in men, after lung cancer, in developed countries.(2) Approximately 15–20% of CRCs are due to a hereditary cancer predisposition.(3) Lynch syndrome (LS) is the most common familial CRC syndrome.(4) Individuals with LS (also referred to as hereditary non-polyposis colorectal cancer or HNPCC) have hereditary (germline) defects in one of their DNA mismatch repair (MMR) genes. MMR deficiency (dMMR) results in an inability to correct DNA replication errors, leading to microsatellite instability (MSI). This deficiency predisposes gene-holders to CRC and other types of cancer. People with LS have a 70% to 80% lifetime risk of developing any type of cancer.(5)

The technology: Gene sequencing (germline testing) is considered to be the gold standard for detection of a germline mutation in MMR genes (dMMR). However, due to the time-consuming nature and considerable economic burden associated with this type of test, the decision to offer germline testing to diagnose LS is commonly made through a stepwise process in order to pre-select patients with higher probability of carrying a MMR mutation.(6;7) This process involves a detailed examination of family history and clinical findings in CRC patients (e.g. the Amsterdam Criteria II (8) or the Revised Bethesda Criteria (9)) and dMMR testing.

dMMR testing is performed to diagnose LS in CRC patients as well as family members of those with confirmed LS, and its ultimate goal is to improve outcomes of the family members who also may have LS and therefore be at increased risk of cancer.(5) This risk reduction can be achieved by genetic testing of potentially affected family members, counselling, cancer surveillance (e.g., frequent colonoscopic or endometrial screening examinations), and prophylactic colorectal or gynecological surgeries in family members. dMMR testing also appears to have utility in the management of CRC by providing prognostic information for patients with stage II tumours.(5) MMR-deficient tumours are associated with improved stage-adjusted disease-free and overall survival rates, and a lower chance of progression, when compared with MMR-proficient tumours.(10) In addition, dMMR status may have a predictive value for the effectiveness of 5-fluorouracil-based adjuvant chemotherapy, favoring MMR-proficient tumors.(10)

Applying the stepwise framework to the evaluation of ethical aspects of dMMR testing

This section will take the reader through the steps that are considered to be essential in our proposed framework; i.e., defining the objectives and scope of the evaluation, stakeholder analysis, assessing organizational capacity, framing ethical evaluation questions, ethical analysis, deliberation, and knowledge translation. Also included are: the central evaluation tasks from the proposed framework in Chapter 4 (Table 4.1- a guide to the stepwise model for ethical evaluation in HTA), along with tips, tools and case study examples, which are presented in boxes. Since the framework presented in Chapter 4 is not meant to be used as a 'how-to guide' for analyzing ethics data, the case study is not centered on the analysis task. For brevity, from here on, the case study on dMMR testing for CRC patients will be referred to as "dMMR study".

Step 1- Defining the objectives and scope of the evaluation

The framework recommends the following tasks:

☐   Clarify objectives and the scope of the HTA project (Box 1);
☐   Consider ethical issues around the HTA project itself (Box 2);
☐   Identify existing knowledge base about the technology (Box 3); and
☐   Specify objectives of the ethical evaluation (Box 4).

These tasks can be accomplished through team meetings, communications with the requestors of the assessment and funding agencies, literature reviews, and consultation with subject-matter experts and stakeholders.

Understanding what the HTA project is about and what the ethical evaluation aims to achieve, as a part of the assessment, is essential for a useful evaluation. It is also important to identify what the results of the assessment will be used for. For example, the primary purpose of the evaluation might be to inform policy decisions about the most appropriate genetic screening test in CRC patients (resource allocation, reimbursements, etc.), practice decisions (guideline development, patient management etc.), or both.

HTA organizations pursuing different types of HTA products may find certain types of assessments more relevant than the others, depending on the degree of their proximity to decision-making. However, regardless of the organizational orientation of the HTA agency and the type of HTA products within which the evaluation results will be presented, the main research objectives often remain the same.(11) Examples of study objectives from dMMR study are shown in Box 1.

We suggest that a careful consideration of ethical issues around the primary motivations for conducting the HTA project is also required at the scoping step, such as special interests of certain stakeholders in the assessment and external pressure from authorities, manufacturers, or patient groups.

Once the scope and purpose of the HTA project are established, existing knowledge and knowledge gaps surrounding the technology of interest should be identified. This can include technological aspects, modes of application, range of possible clinical indications, safety issues, and the therapeutic, economic, or organizational impacts of the technology. Examples of existing information about diagnostic performance, and clinical outcomes of the tests used in the dMMR study are provided in Box 3.

Box 3 - Identify existing knowledge base about the technology

Example:
From the preliminary scoping review, clinical data related to dMMR testing in CRC patients indicates relevant ethical issues:

- The IHC test demonstrated high sensitivity (~ 93%) and specificity (~ 89%) values in diagnosis of LS [*Palomaki et al. Genetics in Medicine 11.1 (2009): 42*]. These values of sensitivity (1-false negative rate) and specificity (1- false positive rate) can be translated to false negative test results in 7% and false positive results in 11 % of the tested CRC patients. False positive results may lead to increased anxiety, unnecessary diagnostic testing or preventive interventions for family members of the tested individual, while false negative results may cause a false sense of security and result in delayed screening and risk reduction activities.
- Considerable (~62%) reduction in mortality risk has been reported in individuals from LS families undergoing prospective asymptomatic screening (colonoscopy or barium enema), compared with individuals from the same families who did not undergo routine surveillance. [*Jarvinen et al. Gastroenterology 108.5 (1995): 1405-1411*] the results of this study highlight the importance of cancer screening and surveillance program in LS families
- The estimated 5 and 10 year overall survival rates are reported to be statistically higher, and recurrence rates to be statistically lower, in patient with MMR deficiency, as compared with MMR proficient patients [*Hveem et al. British Journal of Cancer 110.8 (2014): 2159-2164*]. The better prognosis of CRC patients with deficient MMR confirms the importance of MMR deficiency as a predictive marker of LS.
- dMMR test results can be used as a clinically useful marker for deciding or not deciding to prescribe adjuvant chemotherapy. CRC patients with MMR deficiency have shown tumor resistance to 5-fluorouracil adjuvant chemotherapy [Sargent *et al.* Journal of Clinical Oncology 28.20 (2010): 3219-3226]. The dMMR test seems to beneficial in identifying patients who have a good prognosis without undergoing chemotherapy; i.e., in CRC patients with a positive dMMR test (particularly in stage II cancer) adjuvant chemotherapy, and its related risks and inconvenience, can be avoided.

Identifying the purpose of the ethical evaluation is the next essential task, as it will feed into the type of research questions, study design and ethical analysis approaches. An

example of a purpose statement for ethical evaluation in the dMMR study is provided in Box 4.

Box 4 - Specify objectives of ethical evaluation

Examples of objectives of ethical evaluation

- **To address potential ethical issues involved in the use of dMMR testing for diagnosis of LS in newly diagnosed CRC patients as well as in family members of confirmed LS cases;**
- **To outline important ethical challenges that CRC patients, family members, healthcare practitioners, policy-makers and society may encounter as a result of implementation of dMMR testing or otherwise;**
- **To explore justifiable changes in standards of practice (testing strategies) based on values and preferences of patients and other stakeholders.**

Step 2- Identifying stakeholders

The framework recommends the following tasks:

- ☐ Identify potential stakeholders (Box 5); and
- ☐ Identify the ways in which the stakeholders may affect or be affected by the implementation of the technology (Boxes 6 and 7).

These tasks can be accomplished through brain-storming and/or using other sources of information, such as literature reviews, interviews with key informants and stakeholders, and engaging key stakeholders to identify other stakeholders. However, it should be noted that the extent and the type of information that one may obtain at this step, can be affected by the utilized data collection techniques. For example, surveys may provide more extensive information, while in-depth interviews can lead to a deeper understanding of needs, interests, and the potential impact of stakeholders on the decision about the technology. In a HTA project, stakeholders can be categorized as:

1) Knowledge users, such as regulatory agencies, healthcare policy-makers, governments, healthcare professionals, healthcare researchers or academic sectors;

2) Technology beneficiaries who are targeted to benefit from the candidate technology, such as patients (direct beneficiaries), their family members (direct or indirect beneficiaries), or general public (potential beneficiaries);

3) Technology users, such as hospitals, clinics, and healthcare practitioners; and

4) Technology supporters, such as manufacturers, suppliers and sponsors, funding agencies, or patient advocate groups.

Examples of potential stakeholders in the dMMR study are listed in Box 5.

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Box 5 - Identify potential stakeholders
Potential stakeholders for dMMR study:
- **CRC patients**
- **Patient support groups**
- **Family members**
- **Heath care professionals (family physicians, cancer specialists, medical laboratory professionals, etc.)**
- **Manufacturers/distributers of dMMR testing technologies**
- **HTA-producers (HTA agencies, researchers)**
- **Cancer researchers, practice guideline developers**
- **Healthcare decision-makers**
- **Regulatory agencies (e.g. Health Canada)**
- **National or provincial cancer**
- **Funding agencies (e.g., Ministry of health)**

</div>

Different stakeholders tend to have varying needs and expectations which need to be identified and satisfied in technology design, assessment, decision-making and implementation. In addition, it is beneficial to engage stakeholders who may have some levels of power or interest over the technology in different phases of the HTA. To reach this desired situation, it is important to classify the key stakeholders based on their

potential influence on the implementation of the technology and its consequences (relevance to the technology, legal rights, etc.), as well as their interest area (regulatory, financial, political, health, etc.) and/or interest level (high, medium, low). For any given context, some stakeholders may be more important than others. An example of a summary table for stakeholders' influence/interest description is provided in Box 6. This information can also be plotted in a diagram called "stakeholder power/interest matrix", in which the vertical axis shows the estimated needs and interests of potential stakeholders in the technology, and the horizontal axis indicates their forecasted influence on the decisions regarding the candidate technology (Box 7). The stakeholder power-interest matrix should be built, as early as possible in an evaluation process, before assembling stakeholder groups and involving them in the subsequent steps of the evaluation process (e.g., ethical data collection, analysis, and deliberation).

In situations where stakeholders could not be further engaged in the ethical evaluation through participatory methods, a targeted literature review to identify potential stakeholder values and concerns is strongly recommended.

Box 6 - Identify the ways in which the stakeholders may affect or be affected by the implementation of the technology

An example of stakeholder analysis for dMMR study

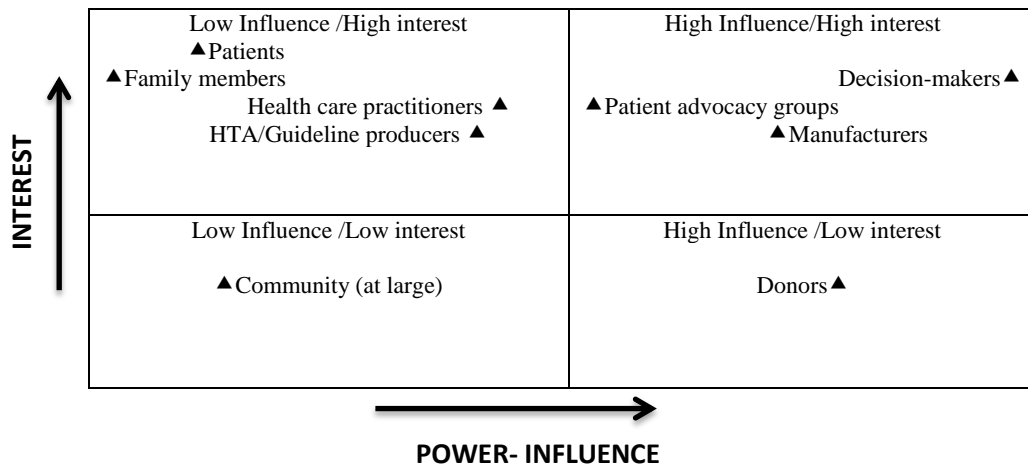| Stakeholders	Type of relationship to the technology assessment	Power level	Interest level
Decision-makers	Authorize/recommend implementation Make decisions on reimbursement policies	High	High
Patients	Direct beneficiaries Ultimate users of the technology	Minimal to moderate	High
Patient/disease related groups	Patient advocates Raise public awareness about important issues around healthcare services, education, etc.	Moderate	High
Family members	Indirect beneficiaries May be affected by the genetic disorder for which the test is used.	Minimal	Moderate/High
Heath care professionals	Technology users Make clinical decisions based on the test results Responsible for implementation of recommendations and guidelines related the technology	Moderate	High
Manufacturers	Technology producers Generate sales/profit	Moderate	High
HTA/Guideline producers (managers)	Control budget and staff resourcing for the HTA project.	Moderate	Moderate
HTA/Guideline producers (researchers)	Knowledge translators Involved in collection, appraisal and analysis of data for the assessment of the technology	Low	Moderate
Community at large	Potential beneficiaries	Low	Low

Box 7 - Identify the ways in which the stakeholders may be affected by the implementation of the technology

An example of stakeholder power/interest matrix for dMMR study

Low Influence /High interest ▲Patients ▲Family members Health care practitioners ▲ HTA/Guideline producers ▲	High Influence/High interest Decision-makers▲ ▲Patient advocacy groups ▲Manufacturers
Low Influence /Low interest ▲Community (at large)	High Influence /Low interest Donors▲

INTEREST (vertical axis)

POWER- INFLUENCE

Step 3- Assessing organizational capacity

The framework recommends the following tasks:

☐ Define key requirements (Box 8); and

☐ Establish a team consisting of ethical expertise, HTA practitioners with experience in evaluation of normative aspects of healthcare technologies, and relevant stakeholders (when needed).

Defining key requirements of an ethical evaluation, such as leadership's support, required knowledge and skills, or time and financial resources can be achieved through team meetings and communications with HTA requestors and funding agencies. Before the HTA team can start an ethical evaluation, required financial support, knowledge, skill sets and opportunities within the organization for hiring new staff and/or training existing HTA team members must be explored. An example of organizational capacity assessment

for the dMMR study in a Canadian academic-based HTA organization with an average of

5-7 research staff and 5 HTA reports per year is provided in Box 8.

Box 8 - Define key requirements

Example:
The following opportunities/ challenges were identified in the organization for ethical evaluation within the dMMR study

Potential support or opposition within the HTA agency
The management and staff are supportive; however, concerns exist about the project timelines and the human and financial resources needed to conduct an ethical analysis.

Project timelines
  – **5 months from the approval of the research protocol to submission of the HTA report**

Availability of required knowledge and expertise

Expertise	Availability	Potential challenges
Ethicist	Not available	Recruiting temporary or permanent researchers, who are capable of performing ethical analysis, should be considered for the purpose of this project.
Information specialist experienced in searching ethical literature	Available	Access to potentially relevant bibliographic databases and Grey literature
Systematic literature reviewers	Available	Training on how to appraise ethical literature might be needed.
Qualitative researchers/ interviewers	Not available	Recruitment of part time researchers may be expensive.
Trainers	Not available	The HTA staff may need to take courses or attend workshops, outside the organization.

Financial and logistical resources needed for conducting an ethical evaluation
Limited

Step 4- Framing ethical evaluation questions

The framework recommends the following tasks:

- Recognize potentially relevant ethical problems and solutions that may arise from the introduction of the technology (Box 9);
- Map the current practice from an ethical perspective (Box 10);
- Identify possible policy/practice implications of the technology (Box 10);

- List ethical issues around the technology (Box 10);
- Justify what issues should be included in the ethical analysis (Box 10); and
- Use dialogues and/or other deliberative methods for input-seeking from ethical and technical experts as well as potential users, if necessary.

These tasks can be accomplished through literature reviews, seeking expert opinion, site visits (observation, review of documents, interviews), and/or using existing checklists for identifying ethical issues around health care technologies (e.g., Hofmann's Socratic approach checklist (12)).

One commonly used way for framing ethical questions is by attending to ethical consequences of implementing a healthcare technology, or otherwise. Questions that use this frame usually emphasize psychological outcomes, technological risk, behavioral or cultural changes, quality of life, outcomes of potentially different medical interventions, consequences of false test results, etc. It is also important to consider ethically challenging or controversial situations, such as requirement for informed consent, testing for identification of genetically susceptible children, or appropriate methods for disclosure of test results. Other issues worthy of consideration are societal expectations, stakeholder preferences and values, cultural norms, patient's rights, as well as implementation and resource allocation issues (equity, access, cost, etc.). Examples of ethical issues that are potentially relevant to dMMR testing are provided in Box 9.

Box 9 - Recognize potentially relevant ethical problems and solutions that may arise from the introduction of the technology

Examples of potentially relevant ethical considerations in the dMMR study
- **Consequences of limiting screening to high risk populations (e.g., those who meet Amsterdam or Bethesda criteria)(8;9)**
- **Adverse consequences of false positive and false negative results: clinical (e.g., unnecessary screening and treatment), psychological (e.g., anxiety, distress, guilt) and economic (e.g., cost of unnecessary testing, screening and treatment)**
- **Privacy and confidentiality issues**
- **Positive and negative consequences of knowing the test results in the families of dMMR positive CRC patients upon knowing the test results (e.g., changes to life style and behavior, family relationships, coping styles, quality of life, etc.)**
- **Need for informed consent prior to dMMR testing**
- **Disclosure of information to children and young people in the affected families**
- **Genetic discrimination (e.g., by employers or insurance companies)**

Note: The above list is not intended to include all possible ethical issues around dMMR testing. There might be many other relevant issues that are not listed here.

In the process of framing ethical evaluation questions, it is essential that team members reflect on which of the identified dilemmas are most relevant to the context and why they should be included in the analysis of ethical issues around the technology of interest. This can be discussed in relation to their impact on current practice, potential policy options, or public acceptability of the technology. An example of a summary table for prioritizing ethical questions is illustrated in Box 10.

Box 10 - Map the current practice; identify possible policy or practice implications of the technology; list ethical issues; and Justify what issues should be included in the ethical analysis

An illustration of prioritizing ethical questions in the dMMR study

Ethical issues	Current practice in Canada	Potential practice issues	Possible policy implications	Reason for inclusion in ethical analysis
Consequences of limiting screening to high risk populations (e.g., those who meet Amsterdam or Bethesda criteria)	The majority of the provinces perform dMMR tests in CRC patients who meet Amsterdam II or Bethesda criteria (high risk populations, or those who are within certain age limits. This may result in missing certain patients.	Risk assessment through applying Revised Bethesda or Amsterdam guidelines may be greatly affected by physician's knowledge and experience.	Rationing of reimbursement decisions Resource allocation Guideline development	Controversial area (universal versus targeted testing)
Clinical, psychological and economic consequences of false positive results	No information was found on the ways of dealing with potential false positive or false negative results of dMMR testing in Canada	Supplementary molecular and germline mutation testing are usually required to confirm the diagnosis. Invasive interventions (e.g., hysterectomy or oophorectomy) or toxic treatments (e.g., chemoprevention to reduce the risk of colon or endometrial cancers) might be administered to suspected cases without further confirmation of diagnosis.	Reimbursement and insurance related decisions. Increased cost and resource utilization	The potential misdiagnosis of LS in families of CRC patients can raise several patient management issues and may result in significant physical, psychological or social harms. Legal implications
Consequences of not following up individuals with false negative results		Physicians may face interpretation challenges where the test results are not consistent with the risk levels in the family. False reassurance of physicians and/or patients, which may affect patient-care giver relationship. Increased morbidity and mortality in false negative cases due to under-diagnosis of LS	Negative public judgement on quality of services (loss of confidence and trust) Diagnostic error research requirements.	
Privacy and confidentiality issues (dealing with information provided by the test)	No information was found on the ways of dMMR-related information disclosure in Canada	Right information might not be made available to all potential beneficiaries of test results. Concerns may exist about ownership of the test results, patient autonomy and confidentiality.	Decisions related to patient information disclosure (conflicting responsibilities). Guideline development. Management of screening and surveillance data.	Legal implications Moral concerns (autonomy, rights and values) Psychological consequences (e.g., creating anxiety, marriage decisions, etc.)
Access and equity issues	The availability of dMMR testing, germline analysis and other testing technologies (e.g., BRAF and MLH1 promotor hypermethylation) varies within and between different provinces. Laboratories in different jurisdictions may not use the same testing methods and eligibility criteria. No information was found on the post-test management strategies for CRC patients and their family members in Canada.	The dMMR tests are not available to all CRC patients, due to the required eligibility criteria for testing in the majority of the Canadian provinces. There might be challenges with the availability of required testing technologies for diagnosis and follow up care of family members who are known or suspected cases of LS (e.g., frequent colonoscopic examinations, or screening for other cancers)..	Development of screening and surveillance programs Resource allocation: justice considerations. Laboratory logistics management.	Concerns about equitable healthcare: certain groups of potential users of technology may suffer due to access issues.

CRC= colorectal cancer; dMMR= mismatch repair deficiency; LS= Lynch syndrome

Step 5- Ethical analysis

The framework recommends the following tasks:

- ☐ Review existing information and acquire additional relevant information through an extensive search of the quantitative and qualitative literature (Box 11);
- ☐ Ensure data from all sources are considered for analysis;
- ☐ Examine the collected data for logic, coherence, validity and reliability (Box 12);
- ☐ Synthesize and integrate collected data (facts and values) into ethical arguments (i.e., apply the principles of biomedical ethics, examine philosophical arguments on the ethical questions from the perspective of different ethical theories, and reflect on possible solutions) (Box 14); and
- ☐ Acknowledge your own values and philosophical interest (Box 15).

As it was mentioned before, the objective of the framework, in general, and this chapter in particular, is not to provide step-by-step instructions on how to perform an ethical analysis. Since selection and application of various ethical analysis methods are context-specific, universal guidelines would not be useful for the analysis of ethical data in HTA. Therefore, our framework assumes that HTA team members who are responsible for ethical analysis have the knowledge and skills to take on this important task. Yet, regular HTA practitioners (non-ethicists) can have a role, although necessarily limited, in ethical evaluation (e.g., helping with formulating ethical questions and searching for potential solution through systematically identifying and summarizing ethics-related data, helping with participatory research, etc.) In what follows, some simple tips are provided in order to help HTA practitioners in performing tasks that are related to ethical analysis.

Traditionally, an ethical analysis consists of making ethical issues explicit by identifying problems, setting out arguments, identifying values, providing reasons, and justifying potential decisions through moral principles and theories. Therefore, in examining each ethical dilemma around the technology of interest, analysts should use their critical thinking as well as problem solving and decision-making skills. A good reason would not be possible without sufficient and valid empirical and/or normative information around the technology. HTA teams are encouraged to collect as much valid and reliable information as possible about the ethical issue in hand. This can be accomplished through systematic identification of relevant empirical and normative data, and scrutinizing the quality of acquired data using appropriate tools. Targeted reviews are often required to fill the information gaps from the previous steps. Box 11 summarizes the literature search process for the purpose of ethical evaluation in the dMMR study. In addition, data collected from different sources or by different methods (empirical and/or normative approaches) should be examined for validity and reliability. The use of McCullough *et al.*'s tool for the appraisal of normative bioethics literature (13) is demonstrated using the dMMR study example, in Box 12.

Box 11 - Review existing information and acquire additional relevant information through an extensive search of the quantitative and qualitative literature

A summary of the review methods used to identify quantitative and qualitative literature:
Literature searches were performed to identify studies that reported quantitative or qualitative data on ethical, legal and social issues around dMMR testing. The following databases were searched: Ovid's MEDLINE (1946-present); EMBASE (1974-2015 current week); the Cochrane Library (2015, current issue); Philosopher's Index and PubMed (for non-Medline records). The main search concepts were dMMR testing and ethical, legal, and psychosocial issues or implementation considerations (technical requirements, staffing, training, accreditation etc.), the search was limited to literature published in the last 5 years.
The identified citations were reviewed for relevance by one reviewer and a second reviewer was consulted, if needed. The search resulted in inclusion of 5 studies. Both empirical and qualitative data on relevant outcomes were extracted.

Box 12 - Examine the collected data for logic and coherence, validity and reliability

An example for the appraisal of normative literature* using McCullough's checklist(13) (summary form)

Checklist	Article#1	Article#2	Article#3	Article#4	Article#5
Focus of the article					
Does the article address a clearly stated and focused ethical issue or problem?	+	++	?	+	+
Is the issue important and why*?	+++	+++	+++	++	+++
Is justification for the importance presented?	+	++	+	+	-
From whose perspective is importance claimed?	authors	authors	authors	authors/ stakeholders	not clear
Validity of the arguments†					
Is the literature search complete?	not clear	++	not clear	not clear	not clear
Are the analysis and argument of cited papers reported clearly and accurately?	+	+	+	+	+
What is the quality of the paper's ethical analysis and argument?	not clear	not clear	not clear	not clear	not clear
Results/Conclusions*					
Usability of the results					
Will the results help me in practice?	+	+	+	+	+
Will the help be practical?	+/?	+	+	++	+
Will the help be theoretic?	++	+	+	+	+
How should the reader change his or her thinking, attitudes, practices, or policies?*	Clinical practice Reimbursement decisions*	Guideline development Clinical practice*	Guideline development Genetic tests information disclosure*	Clinical practice Counselling Genetic tests information disclosure*	Guideline development Clinical practice*

† Although normative ethics data was provided in the included studies, none of them used a normative approach to the analysis of ethics data.

*The information presented in this summary table is drawn from individual appraisal forms

Selected studies:
- Cragun *et al*. Comparing universal Lynch syndrome tumor-screening programs to evaluate associations between implementation strategies and patient follow-through. Genet Med. 2014;16(10):773-82.
- Keogh *et al*. How do researchers manage genetic results in practice? The experience of the multinational Colon Cancer Family Registry. J Community Genet. 2014;5(2):99-108.
- Schneider *et al*. Stakeholder perspectives on implementing a universal Lynch syndrome screening program: a qualitative study of early barriers and facilitators. Genet Med. 2015.
- Lenk *et al*. Different concepts and models of information for family-relevant genetic findings: comparison and ethical analysis. Med Health Care Philos. 2015.
- Gaff *et al.* Process and outcome in communication of genetic information within families: a systematic review. Eur J Hum Genet. 2007;15(10):999-1011.

Next step in ethical analysis is to identify and relate key stakeholders' perspectives on each identified ethical dilemma. Data can be obtained through literature searches and/or primary data collection methods, such as stakeholder surveys, in depth interviews, focus group discussions, etc. In addition to exploring different stakeholders' viewpoints, it is important to reflect on how the implementation of the technology can affect or be affected by their preferences and value systems. It is also beneficial to reflect on the potential ways in which stakeholders would decide or act with regards to each ethical issue.

Then, analysts trained in ethical theory should identify moral principles and theories that might be relevant to the identified issues and decide on modes of reasoning that can be applied to the issue(s). In general, ethical reasoning is the process of identifying, assessing, and developing arguments from a variety of perspectives. Various approaches have been proposed for the purpose of ethical analysis in HTA.(14;15) The most commonly used ethical approaches are summarized in Box 13. To reduce bias and address uncertainties around the candidate technology, it would be helpful to employ more than one approach and to determine if different approaches generate similar results.

In ethical reasoning, it is also essential to identify possible alternatives to the candidate technology (e.g., no testing or using Bethesda criteria only, in the dMMR study) and to carefully apply the same arguments, which were made for or against the use of

technology, to the alternatives. Comparing and contrasting the alternative technologies is

usually helpful in recommending the technology option that is more ethically appropriate,

for example the option that produces the greatest benefit and least harm, or the one that

considers the values and preferences of the greatest number of stakeholders. Examples of

arguments made in relation to dMMR testing versus no testing are illustrated in Box 14.

As mentioned in the previous chapters, the results of an ethical analysis can be affected

by the analysts' background knowledge as well as personal experiences and beliefs. To

minimize the bias that stems from this subjectivity it is suggested that analysts keep self-

reflective notes throughout the ethical evaluation process, from defining the objectives of

the evaluation (step 1) and formulation of research questions to reporting the findings of

the ethical analysis (step 7). Reflective journaling involves recording thoughts,

assumptions and personal values or experiences with the goal of reflecting on them. This

technique can be used as a useful tool for highlighting the analyst's beliefs and

perceptions about potential ethical issues around the technology of interest. This exercise

can bring to light conflicts of interest, and reveal the analyst's pre-existing ideas and/or

misconceptions. The aim of the exercise is not to adopt a "value-free" view of scientific

research, but to acknowledge that ethical analysis and its related tasks are value-laden,

and to encourage HTA-ethics researchers and analysts to be transparent about their own

values in a way that qualitative researchers often do. There might be a complex

interaction between moral obligations of an ethical analyst and his or her choice of

methods or analytical assumptions. Ethical controversies can be difficult to address if

these factors are not clarified. Reflective journaling can offer an opportunity for being

more transparent, especially when dealing with problematic technologies and difficult

choices. Examples of guiding questions that are suggested for reflective journaling (16)

are provided in Box 15.

Box 13 - Commonly used approaches in ethical analysis (see Chapter 2 and reference (14) for more details)

Theory/Approach	Description	Focus	Assumptions
Principlism	Uses ethical principles as general guides for justifying actions and decision making. Four commonly accepted principles of health care ethics, suggested by Beauchamp and Childress,(17) include the principles of respect for autonomy, non-maleficence, beneficence, and justice.	Health Safety Individual rights Justice	Principles are universal and shared by all individuals and groups, regardless of their background and beliefs.
Utilitarian	Uses consequences as the basis for determining the morality of actions and decision making. Actions are judged as ethical if they create the greatest good for the greatest number of people.	Consequences of actions Utility maximization	The end justifies the mean There is usually a prior reference point of "good" for people.
Deontology	Uses duties, rights and the morality of an act (not the consequences it seeks to achieve) as guides for ethical decision making. Actions are judged as ethical or unethical based on the intentions of the actor and inherent rights of individuals.	Dignity Autonomy Freedom Motives	There are generally accepted norms/rules and expected behaviors to resolve ethical dilemmas.
Virtue ethics	Uses virtuous character of individuals who make the choices as a basis for determining the morality of actions and decision making. Actions are judged as ethical or unethical based on the character of the actor.	Honesty / Integrity Fairness Medical professionalism / Competence	Morality of action is insured by having good motivations. Person's action reflects her/his beliefs.
Ethics of care	Uses responsiveness to the needs of others, providing care, preventing harm, and maintaining relationships as the basis for determining the morality of actions and decision making. Actions are judged as ethical or unethical on the basis of attending to the needs and preferences of givers and receivers of care..	Meeting needs Responsibility Responsiveness Competence	Individuals need in necessary need to each other. Individuals' interdependence and maintaining relationship, with other people are basic for human life.
Axiology	Examines the nature of values that are involved in development, implementation and utilization of the technology. Actions are judged as ethical if they serve moral values of professionals, patients, and/or societies within which they are performed.	Professional values Patient/ care giver preferences Societal/cultural values	Morality of action is insured by respecting individual, cultural, or societal norms and values.
Casuistry	Uses analogical reasoning for justifying actions and case-based decision-making. Appropriateness of an action in a particular case is judged by comparing it to a paradigmatic case and with reference to moral considerations that are relevant to that paradigmatic case.	Real world cases Resembling cases Controversial contexts	Information from precedent and existing cases are enough to provide guidance about ethical issues of the technology of interest.
WRE	Examines stakeholders' and citizens' values through an extensive deliberation until a wide and full reflective equilibrium is reached. Appropriateness of an action is judged by establishing coherence between different moral considerations.	Participatory approaches Deliberation Coherence of moral judgements	Moral judgements are subject to revision.

Box 14 - Synthesize and integrate collected data (facts and values) into ethical arguments

A principlist assessment of arguments in relation to using or not using dMMR testing

DMMR testing	No testing	Moral principle/ theory	Stakeholder values	Level of strength
dMMR testing has the potential of informing medical decisions; i.e., knowledge of a positive mutation in CRC patients gives the family members the chance to choose to undergo genetic testing, cancer surveillance and prophylactic treatments, if needed	Since individuals with LS have an increased risk of developing cancer, and in some cases multiple cancers (e.g., colon, endometrium, ovaries, etc.), not using the test may result in higher morbidity and mortality in the affected individuals.	Principles of beneficence and autonomy	Not available	High (supported by strong empirical evidence}
Knowledge of the test results may lead to anxiety or serious long-term psychological effects such as depression in members of LS families.	Not testing is also associated with risk of delayed cancer diagnosis and its consequent physical, psychological and financial costs.	Principle of non-maleficence	Not available	Moderate/ Low (limited facts and value research)
Uneven distribution of dMMR and germline testing facilities among different jurisdictions may limit potential users' access to the technology, especially for family members who live in areas with less access.	Not relevant	Principle of justice	Not available	High (jurisdictional data indicates uneven access)
Family members of a mutation positive CRC patients should be given the choice to seek [or not to seek] genetic testing, cancer surveillance and preventive interventions.	Family members of "not tested" CRC patients should be given a chance to undergo relevant tests to determine their genetic risks, if they consider themselves at risk and are willing to know this information.	Principle of autonomy (also relevant to the rights theory)	Not available	Moderate/low (ethical responsibility to include the argument in the analysis; limited facts and value research)

CRC= colorectal cancer; dMMR= mismatch repair deficiency; LS= Lynch syndrome

Box 15 - Acknowledge your own values and philosophical interest

Guiding questions for reflective journaling (16)

Emotions and Motivation	– Did I think about this case more or less than is typical?
	– Did I think excessively about someone involved in this case?
	– Have I been more or less diligent than is typical?
	– Is my report or opinion narrower or broader than requested?
	– Does my opinion resemble my opinions in other cases?
	– Have I had interpersonal difficulty with other parties connected to this case?
	– Am I having difficulties outside the case?
	– Do others suspect me of bias?
	– Does this case resonate with my sociopolitical beliefs?
	– Do I have pre-existing emotions or motivations about an issue or person related to this case?
	– Have I failed to follow up on discrepancies or details in this case?
	– Have I failed to consider the possibility that mental symptoms are
Fund of Knowledge	– Is my personal background appropriate for this case?
	– Is my training and experience adequate for this case?
Information processing style	– Does my theoretical perspective leave aspects of the case unexplained?
	– Does my reasoning involve unchecked heuristics and biases?

Step 6- Deliberation

The framework recommends the following tasks:

☐ Discuss the results of the evaluation with a group of subject matter (ethics, HTA and clinical) experts to assess their relevance and completeness;

☐ Choose an appropriate method to discuss the results of ethical analysis with relevant stakeholders to seek their feedback on the results (Box 16); and

☐ Seek additional expert insight, if necessary, to ensure the plausibility of the produced results during stakeholder hearings.

Participatory methods have been increasingly considered in the HTA process.(18)

Deliberation involves moving from individual expert-based analyses to reasoned and

critical discussions with other experts, stakeholders and the public in order to fill the information gaps, resolve uncertainties around the technology of interest, and suggest suitable plans of action. Deliberative exercises can often result in the exploration of novel solutions to complex problems, which might not be sufficiently addressed during the analysis step. They can also enable ethical evaluators to:

1) Give a voice to individual preferences, interests and concerns that would not be heard otherwise;

2) Obtain stakeholders' opinion on the relevance of the identified evidence;

3) Hear stakeholders' reasons and arguments for and against potential decisions; and

4) Learn more about stakeholders' past and present experiences, as well as social and cultural diversities and the ways in which these diversities may affect ethical arguments or the evaluation results.

Various methods can be used for obtaining public and stakeholder inputs, including: individual or group interviews, citizens' juries, deliberative polling, consensus conferences and citizens' panels.(19) It would be beneficial to use a range of deliberative techniques to involve a wider range of experts and stakeholders in discussions around the evaluation findings and issues relating to the implementation and utilization of the technology.
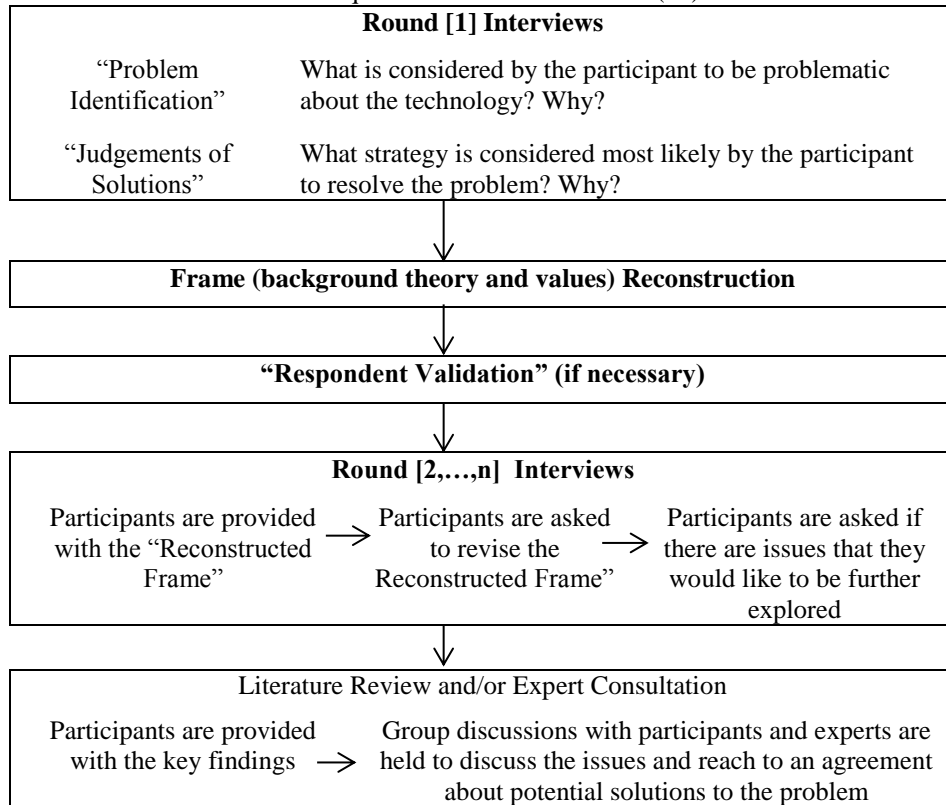
One useful technique that has been cited by van der Wilt *et al.*,(20) originally for the interactive evaluation of cochlear implants for deaf children, is "interpretive frame

reconstruction". This technique is generally used for obtaining perspectives and experiences of the stakeholders on the technology-related problems and their viewpoints about potential solutions or proposed policy interventions. The technique consists of two or more rounds of interviews with stakeholders until a shared construction of the problem and its potential solutions is reached. A summary of this technique is provided in Box 16.

Box 16 - Choose an appropriate method to discuss the results of ethical analysis with relevant stakeholders to seek their feedback on the results

Example:
Interpretive Frame Reconstruction technique for deliberative exercise (20)

Round [1] Interviews	
"Problem Identification"	What is considered by the participant to be problematic about the technology? Why?
"Judgements of Solutions"	What strategy is considered most likely by the participant to resolve the problem? Why?

↓

Frame (background theory and values) Reconstruction

↓

"Respondent Validation" (if necessary)

↓

Round [2,…,n] Interviews

Participants are provided with the "Reconstructed Frame" → Participants are asked to revise the Reconstructed Frame" → Participants are asked if there are issues that they would like to be further explored

↓

Literature Review and/or Expert Consultation

Participants are provided with the key findings → Group discussions with participants and experts are held to discuss the issues and reach to an agreement about potential solutions to the problem

Step 7- Knowledge exchange/ translation

The framework recommends the following tasks:

- Refine your target audience that might be interested in or may benefit from the results of HTA (Box 17);
- Refine information needs of your target audience (Box 17);
- Structure a presentation format to address the information needs of target audience (Box 17);
- Report the results of the ethical analysis in a transparent and effective manner (Box 18); and
- Integrate knowledge translation in all steps of the assessment.

These tasks can be achieved through team meetings, communications with HTA requestors and funding agencies, and consultation with knowledge translation professionals and publishers.

For ethical evaluation results to be useful they must be made available to relevant knowledge users, such as clinical or policy decision-makers, in a timely manner and using appropriate formats. One of the common ways of publishing ethical evaluation results is to integrate them into the HTA report as a separate chapter or under a specific heading. Additional discussion about potential ethical dilemmas may be provided under other aspects of healthcare technologies. For example, discussions about physical or psychological risks of the technology can be included in the assessment of clinical-effectiveness, and equity issues in the economic evaluation sections. An ongoing knowledge exchange between evaluators of different aspects of the technology is desired

throughout the HTA process to enhance the usefulness of the HTA report, including the ethical evaluation results. Examples of information required prior to publishing ethical evaluation results are provided in Box 17.

Box 17 - Refine your target audience and their information needs, and structure a presentation format to address the information needs of target audience

dMMR study knowledge translation plan

Target Audience	– Healthcare policy makers – Clinicians – HTA professionals
Information needs of target audience	– Methods used for ethical analysis – A summary of existing facts and value judgements – Appraisal of ethical data – Potential implications of ethical considerations in the healthcare system – Findings of /recommendations resulting from the ethical analysis
Presentation format	– A chapter in a HTA report, including Introduction, Methods, Results, Discussion and Conclusions.

We suggest, at the minimum, that ethical evaluation reports must cover various dimensions of ethical problems surrounding the technology of interest, while describing details of relevant facts and values from research and non-research sources, as well as methodological approaches used for the collection, appraisal and analysis of ethical data. To increase their usefulness in decision-making for healthcare technologies, ethical evaluation reports should also include the following items:

- Results of stakeholder analysis (if performed) and an explanation of how different stakeholders and members of the public might affect or be affected by implementing, or not implementing, the technology;

- Potential implications of the identified ethical issues in different possible contexts and alternative technologies;

- Possible solutions to ethical problems;

- Information gaps; and

- Suggestions about how to proceed further with the assessment and implementation of the technology.

Box 18 presents a piece of the write up for potential implications of ethical considerations around dMMR testing in the healthcare system.

Box 18 - Report the results of the ethical analysis in a transparent and effective manner

An example of discussion for ethical implications of dMMR testing in the healthcare system

Need for counselling
Due to the sensitive nature of information provided by dMMR and germline testing to diagnose LS and the potential medical and social implications of the test results, dMMR testing should be preceded by genetic counseling sessions.

Informed consent requirement
Since dMMR testing is usually performed on the tumor tissue, patient's informed consent is necessary to obtain test samples through surgery or colonoscopy. Because d-MMR testing may need to be followed by other molecular testing such as the BRAF and/or MLH1 hypermethylation tests, consent should be continuously sought if other tests are going to be performed.

Confidentiality and conflict of responsibilities
Healthcare providers should do all they can reasonably do to make sure that the use of dMMR testing must not affect the autonomous decision-making by the patients and their family members.
Both care-providers and patients may encounter information disclosure dilemmas. On one hand, care-providers are ethically and legally obliged to keep CRC patients' medical information confidential, but on the other hand, they have prima facie obligations to protect "at risk" family members by informing them about their genetic risk. The disclosure of information to family members may be considered by the patients as not respecting the confidentiality principle. The patient's permission should be sought (preferably in a consultation session) before their personal information could be shared with their relatives. CRC patients may consider disclosure of information as their responsibility.

DISCUSSION

In this chapter, the proposed stepwise framework has been applied to the assessment of dMMR testing for patients with CRC. This case study was selected not only because the ethical issues raised by predictive and prognostic genetic testing are clear, timely, and well addressed in ethics literature (e.g., privacy and confidentiality issues, and potential for discrimination), but they also may have more significant policy implications (e.g., provision of counselling services, cancer screening programs for family members, and access issues).

Since recognizing ethical problems that deserve decision-makers attention is critically important in any HTA project, taking a systematic stepwise approach can encourage HTA teams to carefully define ethical issues, alongside other aspects of the candidate technology, collect and use suitable information, apply ethical theories and principles to their analyses, and provide results that are more useful for decision-making. In the majority of HTA-producing organizations, HTA practitioners have traditionally been more familiar with methodological aspects of clinical and economic assessments of healthcare technologies. Therefore, they may find it difficult to incorporate the stepwise ethical evaluation framework into their routine practice. Performing a systematic ethical assessment usually requires time and careful attention as well as skills that may not be readily available in the organization. Ethical evaluation might be viewed as a complex overwhelming task by some HTA practitioners. Team members with less or no previous experience with ethical evaluations may need training and assistance from external

experts to help them conduct the evaluation. In addition, it might not always be possible to go through all the steps due to time or resource constraints. For example, in the dMMR study, it was decided not to take a value research approach to collect primary data on the values and preferences of the identified stakeholder groups. Instead, the published literature was reviewed to identify perspectives of potential stakeholders.

We believe the following tips would be helpful in conducting an effective ethical evaluation:

- Based on the availability of resources, it should be decided whether the ethical evaluation will be conducted by internal, external, or a combination of internal and external teams.

- It is also critical to identify the HTA team members' needs to acquire extra knowledge or to develop new skills.

- There might be overlaps between the ethical evaluation activities and execution of other tasks in the organization. It should be decided prior to the initiation of the evaluation if any of the ethical evaluation tasks should be modified and/ or existing resources should be reallocated, in order to have sufficient capacity for performing the ethical evaluation.

- Relevant guiding questions from the stepwise framework (Table 4.1- a guide to the stepwise model for ethical evaluation in HTA) would allow for handling the complexity of the ethical evaluation.

- To show that an identified ethical problem is important, it is helpful to:

- – Illustrate that the implementation of the technology can cause significant physical, psychological, social harms and benefits, and patient or end-user acceptability;

- – Establish an agreement or consensus among different stakeholders that the technology may have moral consequences; or

- – Prove that certain disadvantaged groups of potential users of the technology may suffer due to the implementation of the technology or otherwise.

- Our framework assumes that ethical analysis requires special intellectual qualifications, and for this reason does not provide any constructs within which ethical reasoning can be performed. However, the questions of if, and how, a detailed guidance should be provided in ethical analysis methods have been envisioned to be included in the framework validation questionnaire (future research).

- At the end of each step, it would be helpful for all working group members to run through the outputs of that step, in a team meeting, before proceeding to the next step.

- All steps should be carried out keeping in mind the needs and values of the end users as well as direct and indirect beneficiaries of the technology (e.g., patients and their family members).

To conclude, the current chapter intends to provide simple and practical tips and examples for HTA team members to integrate ethical evaluation tasks in their routine practice. The instructions and suggestions provided here are not meant to be used as a 'how-to guide' for performing ethical evaluations, but rather they are aimed at helping HTA practitioners touch on key points of the steps proposed by our framework, and the case study example is intended to show suitable utilization of the stepwise framework. It is hoped that this guide will prove to be useful in supporting the evaluation of ethical considerations in HTA as well as enhancing quality.

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CHAPTER 6

Conclusions of the thesis

Summary of findings

The core of this PhD thesis rests in the development of a practical framework to assist

health technology assessment (HTA) practitioners with the evaluation of ethical

considerations of a health technology in a systematic manner. The project was primarily

conducted to construct an action-oriented framework with the goal of reducing the

challenges that HTA producers might face in performing ethical evaluations, and hence

to increase the frequency and efficiency of such evaluations. The secondary objective of

this thesis was to exercise a "procedural guidance development" methodology with

particular attention paid to the normative dimensions of HTA. To reach this goal, we

initially sought answers to three questions:

1) What are the essential procedures and tasks to conduct an ethical evaluation in

HTA?

2) What are the key operational considerations required to perform a successful

ethical evaluation within a HTA organization?

3) How can a practical framework be developed that complies with the

requirements identified in questions 1 and 2?

The first question was addressed through a systematic review of existing guidance documents for ethics in HTA (Chapter 2) (1;2). This review, which used a broad range of bibliographic resources with no limitations of language and year of publication, resulted in the classification of types and areas of focus of ethics frameworks for HTA. In addition, through a content analysis of the identified guidance documents, a list of activities associated with different phases of an ethical evaluation was generated, and potential tools to facilitate an ethical evaluation were identified. The outputs from this review assisted in selecting methodologies and action statements that were appropriate for a comprehensive ethical evaluation, as well as being consistent with different steps of the HTA process.

The second question was dealt with by performing a systematic review of the literature to identify the factors that can facilitate or impede a successful evaluation of ethical considerations through an online survey of HTA agencies around the world (Chapter 3) (3). The results of the review and survey of barriers and facilitators highlighted the importance of using proper scoping mechanisms, provision of resources, choosing appropriate analysis methods, deliberation, and capacity building in ethical evaluation of healthcare technologies. An action-oriented stepwise framework was then drafted based on the key elements of the existing guidance documents and identified barriers and facilitators (Chapter 4) (4).

The framework proposed in Chapter 4 consists of three main components: an algorithmic

diagram, which illustrates different steps of an ethical evaluation throughout the HTA

process, including: defining the objectives and scope of the evaluation, stakeholder

analysis, assessing organizational capacity, framing ethical evaluation questions, ethical

analysis, deliberation, and knowledge translation; a stepwise guide that includes task

statements and guiding questions for each step; and the list of a number of slected tools to

help facilitate the evaluation process (4). An illustrative case study, including

instructions, simple examples, and practical tips supplements the stepwise framework in

order to assist potential users in managing the ethical evaluation process (Chapter 5).

Significance and implications for HTA practice

The significant contributions of this thesis are:

A)   Classification of previously proposed guidance documents for ethics in HTA

based on their methodological features. This comprehensive review, which was published

in 2014, provides ample information about the methodological properties of frameworks

published to guide ethical evaluation in HTA (1;2). Since its publication, the review has

attracted ethics and HTA researchers' attention and has been cited by nine other articles

(3;5-12). It has also been the focus of an insightful editorial written by Bjorn Hofmann

and his colleagues (5). The authors of the editorial have favorably commented on the

thoroughness and breadth of the review. They have invited future researchers to look into

the application of the methodological frameworks to different technological,

organizational, and stakeholder contexts. This article has also been listed in the Selected

Resources section (ethical analysis domain/ guidance publications/handbooks) of the

HTAi Vortal - a web-based source of HTA information published by Health Technology

Assessment international (HTAi) (http://vortal.htai.org).

B)   Identification of factors influencing success and failure of ethical evaluations in

the context of HTA through a systematic review of the literature and an exploratory

survey that consisted of the representatives of diverse groups of national and international

HTA organizations (3). The significance of this study is twofold. First, the study offers

insights on potential drivers and barriers that HTA producers may face in their attempts

to conduct an ethical evaluation. These drivers and barriers have been used for optimizing

the proposed steps for ethical evaluation and their related task statements during the

framework development phase. Second, the survey results create an understanding of

current practice with regard to ethical evaluation across the participating HTA

organizations. This provides a baseline against which the effect of educational or

organizational interventions could be evaluated in future, while highlighting practice

patterns that require additional research.

C)   Development and pilot-testing of a procedural framework for tackling ethical

issues in HTA (4). This framework has a number of unique features which distinguish it

from other frameworks for ethics in HTA.

Firstly, the framework is informed by the key operational features of existing ethical guidelines for HTA, as well as practical concerns and technical demands of potential users. The framework recognizes that ethical evaluations might be discounted or not undertaken in some HTA organizations because they are perceived as being impractical, resource consuming or unfeasible. Therefore, it encourages proper scoping, strategic resource planning, and strengthening organizational capacity.

Secondly, the proposed framework aims to promote a more systematic and structured way of integrating ethics into HTA by mapping the relatively complex process of ethical evaluation and highlighting its main steps. Nonetheless, it is conceptually simple and employs terms and concepts that are familiar to the majority of HTA practitioners, including those who are less familiar with ethical evaluation techniques. The visual representation of the stepwise model simplifies the evaluation process and helps HTA practitioners to understand the nature of an ethical evaluation. The stepwise guide, on the other hand, reduces the complexity of evaluation by breaking down the procedural steps to smaller sets of tasks and providing guiding questions. The framework's supplemental toolbox serves as a support to ensure appropriate ethical evaluations. With its focus on making the evaluation process more understandable and practical for all HTA practitioners, the framework can be easily used in training of HTA professionals. It can also play a role in harmonizing existing evaluation approaches across HTA organizations.

Thirdly, the stepwise framework accommodates the changing relationship between technology assessment, policy, and society by fostering the integration of stakeholder and public input into the ethical evaluation process. Furthermore, it promotes a holistic approach to evaluation and stresses that ethical issues need to be seen in interconnection with clinical, economic, social and legal issues, and that these relationships require an appropriate cooperation between the team members working in different domains of HTA. Another attractive aspect of the stepwise framework is its flexibility. The users of the framework are offered the possibility to choose the tasks that are more relevant to their assessments or to customize the evaluation process according to their needs.

We believe the outputs of this PhD thesis will help to build a more consistent practice of ethical evaluation among HTA professionals.

Limitations and future directions

The current practice of ethical evaluation in HTA faces several challenges: some arise from the paucity of pragmatic methodological guidelines; others stem from misperceptions about value-based evaluations as well as inadequate expertise or institutional support. The purpose of this thesis was to set up the grounds for enhancing the quality and quantity of ethical evaluations in HTA. The framework developed in this research outlines the important steps that should be adopted by HTA practitioners for a comprehensive and effective evaluation of ethical considerations. It also points out the tasks, guiding questions and tools that can support the evaluation process. We believe

that our framework represents an significant response to the issues addressed in the literature about incorporating ethics into HTA, nevertheless there remain limitations to the present thesis project that should be addressed in future research. At the outset, this research work is focused on a "methodology development" process for ethics in HTA and validation of the proposed framework was not in the scope of this thesis. Hence, further formalization of the framework would be realized through implementation and validation processes. We propose several aspects for further research:

From a methodological point of view, validation of the proposed framework is necessary. Two types of validation exercises are envisioned to be used: i) analytical validation, in which subject-matter experts are asked to judge the contents and structure of the framework; and ii) pragmatic validation, in which the framework will be applied to different case studies in order to assess and improve its practicality.

From an applied point of view, the extent to which the validated framework will be implementable and acceptable to HTA producers has to be determined when it is used by mainstream HTA practitioners for "real-world" HTA projects. This kind of research can serve to assess the applicability of the framework to different contexts as well as HTA producers' level of interest to support its future use.

Future research is also needed to further formalize the framework, based on the end-users' needs and demands, and to reach an optimal process for good practice of ethical

evaluation in HTA. Given the diverse contexts within which HTAs are performed, it would not be possible to suggest one-size-fits-all standards. However, some levels of formalization and making the minimum required steps explicit will increase the practicality of the framework and maximize the likelihood that ethical evaluation will become a sustained practice in HTA.

As a final note, to create consistency and encourage good practice in the use of our framework, we urge:

- HTA organizations to create a favorable environment and commit the required technical and financial support;
- HTA practitioners to remain open to the normative evaluation approaches, while helping to build the knowledge and skill capacity for being engaged in such evaluations;
- HTA professionals and ethicists to promote visibility for HTA products that have a well-grounded component on ethics and for the ones that have a remarkable influence on decision-making; and
- Researchers in the area of HTA and health policy to expand the scope of their research to include the questions of whether and how the results of ethical evaluations may impact policy decisions on healthcare technologies.

We hope the contribution of this thesis work will stimulate further research in the field of ethics and HTA.

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