Research Protocol Writing in HTA

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Introduction

The research protocol is an essential part of a research project. A research protocol defines how the assessment will be conducted. The preparation and writing of the research protocol starts after the topic is selected, a policy question[1] is defined and the assessment team is put together. In the following paragraphs, the reader can learn more about the purpose of an HTA protocol and the components which are part of an HTA research protocol.

The purpose of an HTA protocol

The HTA protocol is a full description of the (planned) research and production of the assessment report in the field of HTA. In many cases, the research protocol is also called project plan, whereas the actual research done and the results are documented in an assessment report. The protocol serves as a reference to members of the assessment team to ensure that everyone adheres to the process of creation, the methods and the provisional timeline outlined. The assessment team can be made accountable to the protocol depending on the obligation to follow the project plan, which can vary from HTA institution to HTA institution depending on the purpose of the report.

In most cases, the protocol and the final assessment report are based on templates with common elements and items. These templates vary between countries and institutions as they develop the templates independently with their specific requirements and policy question in mind, which is due to the different health care systems. The EUnetHTA HTA project,[2] for example, is a first pan-European effort to develop common templates for joint assessments.

The use of templates guarantees that the form, structure and content of each research protocol look the same. This standardisation of the protocol helps an efficiency gain in the production and, more important, a fixed and verifiable quality standard. An HTA protocol answers to the following questions (Perleth et al. 2014):

- which aspects and domains should be considered in the assessment
- which information sources should be searched for each chosen domain
- which methods will be used for the assessment of the information sources
- how will the evidence by analysed and summarised

1 The policy question addresses the following aspects: the initiator of the HTA report, the institution which commissioned the assessment, the reason for the timing, the decision to be informed, the recipient/ end-user of the report. In many cases, the elements of the policy questions are recurrent and framed into a statutory health context, e.g. horizon scanning, reimbursement decisions.
2 www.eunethta.eu

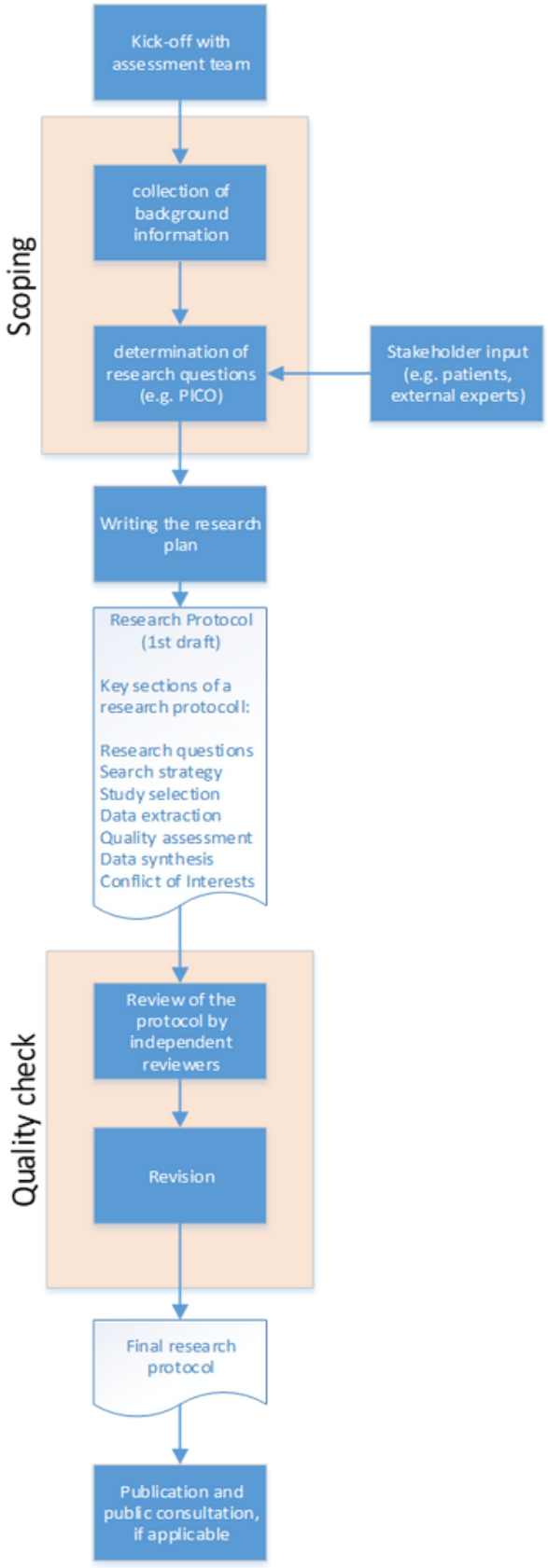
Writing the research protocol

The writing of the research protocol by the assessment team happens after the formulation of the policy question and the establishment of the assessment team and ends with the publication of the protocol. In some cases, the protocol needs approval by executive bodies within the agency or a consultation of stakeholders (e.g. patients, service users) may follow. The assessment team is composed of the authoring team and the dedicated reviewers who check the project plan.

If, during the development of the protocol the research questions have altered, this needs to be agreed with the commissioning body before the work starts. Modifications to the protocol may arise from a clearer understanding of the research question. Any modification to the protocol should be clearly documented and justified in the assessment report and in a protocol addendum.

The writing of the protocol itself can be separated in different schematic steps: kick-off, scoping, writing the protocol by the authoring team, review of the protocol by dedicated reviewers and other stakeholders (e.g. patients, external experts), revision, approval and publication, sometimes complemented by a consultation of stakeholders. All steps follow a predefined time plan.

Figure 1. Example of a process of writing a research protocol



Problem description and background information

An HTA protocol starts in a first section with the problem description and the presentation of the background information about the health problem at stake and the technology. Based on this information, further research questions crystallise. Both steps, which are described here consecutively, actually happen at the same time. The background information can address the following aspects for example:

- Characteristics of health problem and illness
- Epidemiology, prevalence
- Alternative treatments
- Current medical standard of therapy/ diagnosis
- Description of the technology (status of the technology)

Table 1. Background information about the health problem and patient population (Perleth 2014)

Question	Example
Health problem	Illness Condition
How does the illness work?	Aetiology, pathology
How does the illness develop and progress?	Presentation of symptoms, stage of illness and progression
Which are the consequences?	Disabilities, symptoms, health-related quality of life, death
Alternative ways of treatment	Drug Operation Current standard of intervention
Population (epidemiology and burden of disease)	Patients Healthy individuals
How many persons are affected?	Incidence and prevalence
Who is affected?	Age Sex Risk factors Socio-economic factors

Table 2. Background information about the health problem and patient population (Perleth 2014)

Question	Aspects
How does the technology work?	Drug or medical device, technical characteristics
What are the prerequisites of an application?	Prerequisite for application, qualifications, maintenance
What is the status of the technology?	Marketing Degree of use Fields of application Current regulations Manufacturers Benefits and costs

In order to generate background information, authors can conduct preliminary scientific literature searches for orientation. These searches are not comparable to systematic searches aimed at providing the answers to the research questions.

Definition of the research question

Based on the background information, the aim of this step in the HTA assessment is to identify important aspects and domains for the assessment in order to specify the research questions and scope of the assessment. Another term for the preparation of the assessment (collecting background information, defining research questions is therefore 'scoping'). If the HTA assessment is depicted in phases, the definition of the research question takes place in the scoping phase of the assessment, followed by the development of the project plan (see figure 1), whereas the phases are overlapping.

The following nine domains can be subject to an assessment including the aspects covered by the background information:

- Health problem, epidemiology, prevalence, alternative treatments, Current medical standard of therapy/ diagnosis
- Characteristics of the technology
- Safety
- Effectiveness,
- Cost-effectiveness,
- Ethical aspects
- Patient and social aspects,
- Legal aspects and
- Organizational aspects

Moreover, the research question should identify, inter alia, he intervention to be assessed, the comparators to be considered, the outcome criteria according to which the benefits of the technology will be measured, and the patient population to which the intervention and its comparators are applied. The so-called PICO model summarizes all these aspects and is a strategy for formulating questions and search strategies. PICO stands for four different potential components of a research question [3]:

PICO

- P = Patient, population, or problem (e.g. age, sex, illness)
- I = Intervention, (= pharmaceutical, diagnostic or therapeutic procedure)
- C = Comparison (= comparator, e.g. current medical standard in treating the illness)
- O = Outcome (= patient-relevant endpoints, e.g. survival)

The classic PICO question may be extended by:

- S = Study design (= study type, e.g. randomised controlled trials, non-randomised controlled trials)

The PICO schema determines which studies are going to be considered in the data analysis: the study selection follows the criteria agreed on by the research questions. Therefore, in practice, other criteria can also be decisive in selecting studies (e.g. further requirements to be met by the study, setting of a study, language, type of publication, and period of publication). In the course of an assessment, it can always become apparent that the criteria need to be adapted which is then justified in the assessment report.

Research questions should be clearly formulated, answerable, restricted in quantity, consider patient-relevant endpoints and relevant comparators. The selection of domains and the PICO question(s) determine the following research plan and strategy.

Involvement of external stakeholders in the scoping phase

When drawing up the research question, the assessment team can ask for the expertise of external stakeholders: When determining the outcomes to be analyzed, it can be helpful to involve patients who are living with the condition in question, in order to ensure that the outcomes are important and relevant from a patient's point of view.

3 https://linkeddata.cochrane.org/pico-ontology

Moreover, they may have information on the disease and treatment process, which is not accessible to the assessors through the evaluation of clinical studies. If the patient is not able to communicate, as a result of the illness or because of being a child, a caregivers' perspective may be useful in such cases.

The way of involving patients in the scoping phase can take various forms: e.g. questionnaire, (telephone) interviews. Patients can be consulted regarding the following aspects:

- their disease/condition and their unmet needs,
- currently available treatments,
- expectations with respect to new treatments (e.g. fewer side effects),
- identification of subgroups and possible effect modifiers,
- quality of life issues,
- target treatment population and risks of off-label use

By involving external experts, the HTA assessors gain an overview in the medical context, in which the pharmaceutical or the medical device will be applied. A consultation of external experts at this moment in the assessment process, allows identifying relevant issues at an early stage, which need to be considered in the assessment of the technology. During the scoping phase, the following topics may be included in a questionnaire to be distributed to the experts:

- illness and effects of the illness
- aims of therapy
- patient in daily care
- therapy options (drug and non-drug)
- therapeutic need beyond the existing therapy options
- status of the current medical standard

There are other ways for involving external experts in the assessment: they accompany the assessment process and are at the disposal of the assessment team if it has questions regarding the condition and related aspects.

There are examples of involvement of manufacturers in HTA processes (e.g. France, EUnetHTA). By the so-called 'fact check" manufacturers can check if the data they submitted are displayed correctly. The involvement of manufacturers in assessment is a contentious issue and would demand a chapter of its own. The main point is the strict requirement of guaranteeing the independence and objectivity of the assessment team and the HTA report.

Research plan to answer the research questions

After having outlined the background information, the scope and PICO, the description of the search strategy follows in a second section. This part presents the selected information sources and search strategies for the assessment.

A following section explains the procedure for study selection (2-stage procedure or 3-stage procedure with four-eyes-check) and the procedure for data extraction. This goes into further detail, for example the protocol could specify whether authors of primary studies be contacted to provide missing or additional data.

The protocol describes which methods of data analysis and synthesis will be applied (e.g. risk of bias assessment, meta-analysis, sensitivity analysis, analysis of subgroups and effect modifier). As analyses will depend on what data are available, and because it is difficult to anticipate all of the statistical issues that may arise, it can be difficult to pre-specify full details of the planned synthesis. Therefore, the need of adapting the protocol may occur. Any change in the protocol has to be reasoned and documented with strict demands on quality and transparency.

The project plan ends with a list of literature collected during the preliminary literature search for generating the background information and determining the research questions.

The HTA protocol also contains a section on the time-plan for the assessment and the conflicts of interest of the involved parties to the assessment. As the study selection and data extraction and review of the protocol are commonly executed by several researchers, a procedure on how to solve disagreements between the involved parties needs to be described in the protocol.

Review of the research protocol as quality check

The reviewers are part of the assessment team and are selected when it is appointed at the beginning of the project. The reviewers should work independently from the authoring team.

The review of the research protocol ideally is based on a set of review questions:

- the readability and completeness of the document,
- the consistency of terminology,
- the adherence to applicable guidelines,
- the check of information retrieval strategy,

- the consistency of inclusion and exclusion criteria for study selection,
- the check if the process of stakeholder involvement (patients, external experts) is described appropriately,
- the check of the timelines (feasible, correct).

Finally, external experts may also review the research protocol at the same time as the reviewers or after them.

Publication of the HTA protocol and consultation

The research protocol is published in the internet. In this way, the assessment team can be held accountable for what it has planned to do in relation to what it reports in the final report. Since assessments conducted by public bodies have an impact on budget decisions and affect a wide range of stakeholders, a publication of the research protocol answers to calls for transparency. Moreover, a public consultation of the protocol might be considered. External stakeholders may make helpful statements on the research protocol, for consideration by the assessment team.

Bibliographic sources and suggested readings

Perleth et al. 2014. The Perleth 2014 reference is in German hand had not been translated unfortunately. We will check for English references.

www.eunethta.eu.

https://linkeddata.cochrane.org/pico-ontology