HTA 101: Essential Information for Newcomers

Author: Clifford Goodman
Health technology
A health technology is defined as an intervention developed to prevent, diagnose or treat medical conditions; promote health; provide rehabilitation; or organize healthcare delivery. The intervention can be a test, device, medicine, vaccine, procedure, program or system [http://htaglossary.net/health-technology].

Health technologies can be described in terms of their physical nature, clinical purpose, stage of development or diffusion.

Physical nature:
- Drugs: e.g., aspirin, antibiotics, cancer chemotherapy
- Biologics: e.g., vaccines, blood products, biotechnology-derived substances
- Devices, equipment, supplies: e.g., cardiac pacemaker, MRI scanner, mosquito netting
- Medical and surgical procedures: e.g., acupuncture, bariatric surgery, cesarean section
- Public health programs: e.g., water purification system, vaccination program, smoking prevention program
- Support systems: e.g., clinical laboratory, drug formulary, electronic health record system
- Organizational, delivery, managerial systems: e.g., primary care network, health care payment system

Clinical purpose:
- Prevention
- Screening
- Diagnosis
- Treatment
- Rehabilitation
- Palliation
Stage of development or diffusion:
- Future
- Experimental (laboratory or animal testing)
- Investigational (clinical studies, i.e., in people)
- Established (standard approach)
- Obsolete

**Health Technology Assessment and its Role in Health Care**

**Origins of Technology Assessment**

Technology assessment (TA) arose in the mid-1960s from an appreciation of the critical role of technology in modern society and its potential for unintended, and sometimes harmful, consequences. The term “technology assessment” was introduced in 1965 in the US House of Representatives, with the primary purpose of serving policymaking. Examples of early assessment topics were offshore oil drilling, pesticides, automobile pollution, nuclear power plants, supersonic airplanes, and the artificial heart.

Development of TA in 1960s and 1970s coincided with the introduction of health technologies that prompted widespread interest in matters that transcended their intended health effects. Examples of topics of early HTAs include: multiphasic health screening; in vitro fertilization; predetermination of the sex of children; slowing of aging; modifying human behavior by neurosurgical, electrical or pharmaceutical means; and drug bioequivalence.

**Health Technology Assessment**

HTA can be defined as follows:
- HTA is the systematic evaluation of properties, effects, or other impacts of health care technology.
- The main purpose of HTA is to inform policy making for technology in health care.
- HTA may address the direct and intended consequences of technologies, as well as the indirect and unintended consequences of technologies.
- HTA is conducted by interdisciplinary groups.
- HTA uses explicit analytical frameworks and a variety of methods.
In 2020, a joint task force of INAHTA and HTAi developed a definition of HTA as follows:

“HTA is a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle. The purpose is to inform decision-making in order to promote an equitable, efficient, and high-quality health system.” (O’Rourke et al. 2020)

HTA is used to inform various functions. It is essential to understand that HTA usually does not generate a policy or decision; instead, it informs policies or decisions made by others. In particular, HTA is used to:

- Advise payers (health authorities, health plans, etc.) about technology reimbursement: coverage, coding, and payment amounts
- Advise/guide clinicians and patients about technology use (e.g., with evidence-based clinical practice guidelines)
- Help managers of hospitals, health care networks, other provider institutions/organizations to make decisions about acquiring or investing in technology
- Support decisions by national and regional public health authorities about conducting population health programs

Also, HTA can be used to:

- Support decisions by health technology companies about technology development and marketing
- Support decisions by investors in the health care sector
- Inform research agencies about evidence gaps, unmet needs

Related Concepts
There is a variety of methods, sources of evidence, and concepts that can be related to HTA or interact with HTA. Among these are:

- Outcomes research
- Patient-centered outcomes research
- Real-world evidence
- Comparative effectiveness research
- Systematic review
- Meta-analysis
- Pharmacoeconomics

1 http://htaglossary.net/health-technology-assessment
Demand for HTA
Multiple factors contribute to the demand for HTA. Among these are:

- Aging populations
- Increases in chronic disease
- Growth of the middle class in developing nations
- Growth in patient/consumer demand for health information
- Ongoing development and marketing of new drugs, biologics, diagnostics, devices, other technology
- Public attention to high-priced technologies (e.g., for cancer care, rare diseases)
- Large variations in health care practice
- Inappropriate use of health care technologies, including over-use, under-use, and improper use
- “Off-label” uses (i.e., not approved by regulatory agency) of drugs, biologics, devices
- Rising health care costs (constraining resources for other important needs)
- Major reforms of national and regional health care systems
- Concerns about social, ethical, legal impacts of health technology

Unintended and Intended Consequences
Consistent with the origins of TA, health technologies can have unintended consequences/effects as well as their intended ones. Unintended consequences can be beneficial or harmful. HTA seeks to anticipate and examine their implications. Some examples of technologies with unintended consequences in some patients are:

- Aspirin: anticoagulation
- Bariatric surgery: cure for diabetes
- Antibiotics: overuse and improper use resulting in multi-drug resistant bacterial strains
- Highly active anti-retroviral therapy (HAART) for HIV/AIDS: increase in high-risk behaviors
- Medical ultrasound: fetal sex selection
- Prostate-specific antigen (PSA) testing: unnecessary invasive testing, therapies, and adverse effects for some men
**Inappropriate Use**
Inappropriate use of technology can call attention to the need for HTA. It can occur in different ways, including:
- Over-use: used in patients who are not indicated (i.e., for whom there is no evidence of benefit), or used too frequently in those patients
- Under-use: not used in patients who are indicated, or used too infrequently in those patients
- Improper use: although used in patients who are indicated, used incorrectly (e.g., incorrect surgical technique, incorrect drug dosing, incorrect radiation exposure)

**Diffusion of Ineffective or Harmful Technologies**
The history of health care technology includes many instances in which technologies became widely used with inadequate or even falsified evidence, only to be discovered later to have serious adverse health effects in at least some patients. Among the many examples are:
- Autologous bone marrow transplantation with high-dose chemotherapy for breast cancer
- Antiarrhythmic drugs
- COX-2 (cyclo-oxygenase-2) inhibitors for patients at risk for heart disease, stroke, and certain other conditions
- Hormone replacement therapy for healthy menopausal women
- Intermittent positive pressure breathing
- Magnetic resonance imaging (MRI) for low back pain in first 6 weeks
- Oxygen supplementation for premature infants
- Prefrontal lobotomy for mental disturbances
- Prostate specific antigen (PSA) screening for prostate cancer
- Radiation therapy for acne
- Thalidomide for sedation in pregnant women

These and other examples of technologies, including some in current use, call attention to the need to conduct methodologically rigorous HTA in a timely manner.

**Properties and Impacts Assessed**
What does HTA assess? The main properties and impacts assessed include:
- Technical: conformity with design, performance characteristics, e.g., pharmacodynamics, diagnostic test accuracy
• Safety: judgment of the acceptability of risk (probability and severity of an adverse outcome) associated with using a technology in a given situation
• Efficacy and effectiveness: how well a technology achieves its intended purpose, especially in health outcomes
• Cost and other economic: microeconomic, e.g., cost-effectiveness of particular technologies, cost burden on patients; macroeconomic, e.g., impact on national health care costs, gross domestic product, employment, resource allocation across health care and other industrial sectors
• Ethical, legal, patient and citizen, and political: impacts on or challenges to normative concepts (e.g., valuation of human life, equity); choices about how and when to use technologies; research and the advancement of knowledge; resource allocation

Efficacy vs. Effectiveness
HTA makes an essential distinction between these terms:
• Efficacy: benefit of using a technology for a particular health problem in ideal conditions of use, for example, in a strict protocol of a randomized controlled trial or at a “center of excellence."
• Effectiveness: Benefit of using a technology for a particular health problem in general or routine conditions of use, for example, in a community hospital.
• Among the main categories of health outcomes that are used to assess efficacy and effectiveness are:
  • Mortality (death rate)
  • Morbidity (disease rate)
  • Adverse health events (e.g., harmful side effects)
  • Quality of life
  • Functional status
  • Patient satisfaction

Biomarkers and Surrogate Endpoints:
A biomarker (or biological marker) is an objectively measured characteristic (such as from a laboratory test or radiological image) that is used as an indicator of normal biological processes, natural history of disease, or effect of a therapy. Examples:
• Blood pressure
• EKG (electrocardiogram)
• Bone density
• Hemoglobin A1c
Biomarkers are not health outcomes (or endpoints). However, when a biomarker is closely associated with a health outcome (or clinical endpoint), and particularly when it is predictive of a health outcome, it can be a surrogate endpoint. Example:

- Decreased blood pressure for decreased risk of stroke
- White spots on an MRI scan for multiple sclerosis lesions

**Patient-Centered Outcomes**

Patient-centered outcomes and patient-reported outcomes are increasingly important in contributing to evidence that informs care decisions by clinicians and patients, and coverage policies of payers.

Patient-centered outcomes are those that patients experience in real-world settings, including: survival, functional status, quality of life, quality of death, symptoms, pain, nausea, psychosocial well-being, health utility (patient-perceived value of particular states of health), and patient satisfaction. Can be assessed at a generic level or a disease/condition-specific level.

Patient-reported outcomes are those that are self-reported by patients or obtained from patients (or reported on their behalf by their caregivers or surrogates) by an interviewer without interpretation or modification of the patient’s response by other people, including clinicians.

Examples of generic patient-centered outcomes include the following (of which there are multiple versions):

- EuroQol (EQ-5D)
- Health Utilities Index
- Nottingham Health Profile
- Quality of Well-Being Scale
- Short Form (12) Health Survey (SF-12), Short Form (36) Health Survey (SF-36)
- Sickness Impact Profile

Examples of disease-specific patient centered outcomes in multiple sclerosis:

- Multiple Sclerosis Quality of Life Inventory (MSQLI)
- Multiple Sclerosis Quality of Life-54 scale (MSQoL-54)
- Functional Assessment of Multiple Sclerosis (FAMS)
- Multiple Sclerosis Impact Scale (MSIS-29)
- Leeds Multiple Sclerosis Quality of Life scale (LMSQoL).
Hybrid or Combination Outcomes

Another category of health outcomes used in HTA is aggregated outcome measure. These are measures of health improvement (or loss) that combine survival and morbidity (including mortality/survival, quality of life, or functional status) into a single unit:

- QALYs: quality-adjusted life years
- DALYs: disability-adjusted life years
- HYE: healthy-years equivalents

A strength of these outcomes is that they enable comparisons of the impact of health care or other changes (e.g., environmental or economic) where the outcomes (other than survival) are not the same, e.g., incidence of diabetes, reduction in heart attacks, or prevalence of tobacco use. They are based on somewhat different assumptions and methods (e.g., for determining quality of life and disability).

QALYs are used more often in cost utility analyses to determine ratio of change in cost to QALYs gained from using a particular health care technology. DALYs are used more often in public health to measure population disease burden and impact of health programs on population health.

Some basic principles of QALYs are:

- It is widely accepted that one year of life spent in a good state of health (or function of quality of life) is preferred to one year spent in a poor state of health.
- “Utility” refers to the relative preference (value) that an individual (or society) has for a particular state of health.
- Utility weights are determined using direct methods, e.g., time trade-off or standard gamble, or indirect methods, e.g., SF-36, EQ-5D, Health Utility Index, Quality of Well-Being Scale.*
- The QALY is a unit for measuring outcomes of health care (or other interventions). QALYs combine length of life with quality of life. That is, years of life are adjusted (weighted) by patient/user utility for the quality of life experienced during those years.
- The QALY may be used as the unit of patient/user outcomes in a cost-utility analysis.
Primary data methods involve collection of original data, for example, using experimental designs (e.g., randomized clinical trials) or non-experimental designs such as observational studies (prospective or retrospective). Most HTAs do not involve conducting primary data collection, but they use evidence from available primary data studies.

Secondary / integrative analyses combine data from existing sources, e.g., systematic reviews, meta-analyses, modeling. Most HTAs involve conducting one or more of these methods; some HTAs also involve using evidence from available integrative studies.

Economic analyses involve various techniques of weighing costs and benefits (outcomes or other results). Many HTAs involve one or more of these analyses.

**HTA Methods**

Three main categories of methods used in HTA are: primary data collection, secondary (integrative) methods, and economic analyses:

- Primary data methods involve collection of original data, for example, using experimental designs (e.g., randomized clinical trials) or non-experimental designs such as observational studies (prospective or retrospective). Most HTAs do not involve conducting primary data collection, but they use evidence from available primary data studies.
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- Economic analyses involve various techniques of weighing costs and benefits (outcomes or other results). Many HTAs involve one or more of these analyses.

**Primary Data Methods**

When HTAs examine evidence from primary data studies, they consider attributes associated with stronger or weaker evidence for determining the causal effect of a technology on outcomes (e.g., efficacy or effectiveness and safety). In general:

- Prospective studies > retrospective studies
- Interventional studies > observational studies
- Controlled studies > uncontrolled studies

**QALY = Length of Life X Quality Weight**

Using QALYs to capture changes in length of life (survival) and quality of life (e.g., utility for state of health) resulting from new or additional treatment.
Studies with contemporaneous control groups > studies with historical control groups
Studies with randomized assignment of patients to treatment and control groups > studies with non-random assignment.
Large studies (with enough patients to detect true treatment effects) > small studies
Blinded studies (patients, providers do not know which intervention is being used) > unblinded studies

Primary data methods include experimental and non-experimental designs. Main types of experimental designs include:
- Randomized controlled trial (RCT)
- Randomized cross-over trial
- N-of-1-trial
- Group randomized trial
- Non-randomized controlled trial*
- Pragmatic trials (randomized or non-randomized)

A controlled trial in which participants are assigned to treatment and control groups using a method other than randomization, yet intended to form similar groups. Sometimes known as a “quasi-experimental” design.
The diverse types of non-experimental designs include:
- Prospective cohort
- Retrospective cohort
- Case-control
- Cross-sectional
- Interrupted time series with comparison
- Non-concurrent cohort
- Interrupted time series without comparison
- Before-and-after
- Time series
- Case Series
- Case study
Evidence Hierarchies
HTA organizations (and others) use various evidence hierarchies or frameworks to rate the quality of individual studies and bodies of evidence (groups of studies). Most of these are based on, or start with, principles of stronger vs. weaker evidence for establishing causal effects of a technology, as noted above. Different types of evidence questions call for different evidence hierarchies. For example, evidence hierarchies for questions about disease prevalence, diagnostic accuracy, or detecting rare adverse events will differ from evidence hierarchies for efficacy/effectiveness of treatments. A basic example of an evidence hierarchy for therapies is:

- Systematic reviews and meta-analyses of RCTs
- Randomized controlled trials (RCTs)
- Non-randomized controlled trials
- Prospective observational studies
- Retrospective observational studies
- Expert opinion

There are many versions of such hierarchies, including some with more extensive levels/breakdowns.

A weakness of such hierarchies is that, while they tend to reflect internal validity of a cause-and-effect relationship between a technology and one or more outcomes (e.g., mortality, morbidity), they do not generally reflect external validity (generalizability) of the evidence to more diverse patients and care settings.

Secondary or Integrative Methods
The main categories of secondary methods, which combine or integrate data from primary data studies, include:

- Systematic literature review
- Meta-analysis
- Modeling (e.g., decision trees, Markov models)
- Group judgment (“consensus development”)
- Unstructured literature review
- Expert opinion
The set of methods shown above is not arranged in a hierarchy. However, the general trend in HTA is to rely on systematic reviews, meta-analyses, and modeling. Unstructured literature reviews are not considered good practice in HTA, because they are especially subject to biases that can diminish the credibility of HTA findings. Although expert perspectives are an important part of certain aspects of HTA, the use of expert opinion as the main method for conducting HTA is not considered good practice in HTA.

Systematic Literature Review
A systematic literature review (or systematic review) is a form of structured literature review that addresses one or more evidence questions that are formulated to be answered by analysis of evidence. Systematic reviews involve:

- development of evidence questions (or “key questions”) that are intended to capture the body of evidence to be assessed
- an objective means of searching the literature, typically using prospectively designed automated searches of bibliographic databases (usually peer-reviewed literature and selected other sources, including “grey literature” as appropriate for an assessment topic)
- applying predetermined inclusion and exclusion criteria to this literature derived from the search
- critically appraising the relevant included literature
- extraction and synthesis of data and information from relevant body of evidence base to formulate answers to the evidence questions
- A systematic review may include one or more meta-analyses.

Systematic reviews differ from unstructured literature reviews in multiple ways. Most systematic reviews start with focused evidence questions, have predefined literature search and inclusion/exclusion criteria to identify relevant evidence, include a detailed description of the methods used, are quantitative (accounting for the numbers of articles retrieved from the initial searches and numbers of articles excluded consistent with predefined criteria), and are reproducible. In contrast, a traditional or unstructured literature review may have broad or poorly defined methods section, be less likely to be quantitative, and not be reproducible.
Most systematic reviews use a format for defining a set of evidence questions and related parameters that define the evidence base for the HTA. A commonly used approach is:

**PICOTS**

- **P**: Patient, population, or problem of interest
- **I**: Intervention or exposure
- **C**: Comparator (basis of comparison, e.g., standard of care, control group)
- **O**: Outcomes (primary or secondary endpoints, e.g., mortality, morbidity, quality of life)
- **T**: Timing (duration of intervention or follow-up period of data collection, if applicable)
- **S**: Setting (location of delivery of intervention, e.g., inpatient, outpatient, home)

For example, an evidence question about treatment for hypertension could be expressed in the following PICOTS format:

- **Population**: males and females age 55-75 years with mild hypertension
  - diastolic blood pressure 85-99 mm Hg
  - systolic blood pressure 130-159 mm Hg
  - no other serious health problems
- **Intervention**: standardized, moderate exercise program
- **Comparator**: usual physical routine and diet
- **Outcomes**: changes in:
  - general and abdominal obesity
  - systolic blood pressure
  - diastolic blood pressure
  - aerobic fitness
- **Timing**: 6-24 months follow-up
- **Setting**: outpatient (clinics, physician offices)
Meta-Analysis
Meta-analysis refers to statistical procedures for combining results from different studies. This combination may produce a stronger conclusion than can be provided by any single study. Meta-analysis is generally most appropriate when there are not definitive studies on a topic (e.g., when their sample sizes are too small) and non-definitive studies are in some disagreement (e.g., when their treatment effects are contradictory or show large variance). The purposes of meta-analysis include:
- Encourage systematic organization of evidence
- Increase statistical power for primary end points and general applicability of findings
- Resolve uncertainty when reports disagree
- Provide quantitative estimate of effect (e.g., effect size or odds ratio)
- Answer questions not posed at the start of individual trials
- Identify needs and planning for major trials

Certainly, meta-analyses can be very useful in synthesizing evidence from multiple sources. However, like other forms of analysis, they can have weaknesses. These may include: publication bias of the primary studies comprising the meta-analysis, biased selection of available relevant studies, poor quality of the primary studies, unexplainable heterogeneity across the studies (differences in, e.g., study populations, delivery/dosage of the interventions or comparators, or how outcomes were measured), and biased interpretation of findings by the authors.

In recent years, there has been increased interest in applying meta-analysis in circumstances in which there are insufficient direct (“head-to-head”) comparisons of technologies. Network meta-analysis is a type of meta-analysis in which multiple (three or more) alternative technologies are compared when there are limited or no available “head-to-head” trials of those technologies. This enables integration of data from available direct trials and from indirect comparisons across trials based on a common comparator, which could be a placebo or standard care. Network meta-analysis is also known as “multiple-treatment” or “mixed-treatment comparisons meta-analysis.”
Modeling
In HTA, modeling refers to analytical techniques for simulating (representing) real processes involving decisions and their outcomes. For example, in determining which technology or regimen option is more effective or cost-effective for a particular patient population, modeling can account for the uncertainties (probabilities) that each option or decision will result in particular outcomes (e.g., health states), and/or the value (e.g., patient utility, cost-effectiveness) associated with each outcome.

Among the main types of modeling used in HTA are: Markov modeling; decision tree; multi-criteria decision analysis; Monte Carlo simulation; and various simulations of disease processes, health care interventions, and health care systems. For example, Markov modeling represents changes from one state of health to another, such as different stages of disease and death. This type of modeling is useful for representing patient or population experience when: health states change over time, some or all of the health states may recur, and there are known probabilities of transition across health states. Markov modeling assumes that each patient is in one of a set of mutually exclusive and exhaustive health states for a given period of time, there is a set of allowable (i.e., non-zero) probabilities of moving from one health state to another (including remaining in the same state from one period to another), and patient utilities and costs can be assigned to each health state.

Shown below is a general hypothetical example of a Markov modeling in which there are four possible health states: normal, asymptomatic disease, progressive disease, and death. Transition probabilities are shown for one-year periods. In this example, a baseline population of 100,000 is followed for two years (i.e., year 0 to year 2) as is progresses through the transition probabilities. A model such as this could be made more complex, such as if the transition probabilities were to differ for patient subgroups (e.g., by age, sex, or comorbidities).

Markov Modeling Disease States and Transition Probabilities (Annual, Year 0 to Year 2)
Economic Analyses
HTA can use various types of economic analyses. Each of these has different purposes. Any particular HTA may include one or more of these. The main types include:

- Cost effectiveness analysis (CEA): costs weighed against outcomes focused on a single natural unit, e.g., deaths, heart attacks, lung cancer cases
- Cost utility analysis (CUA): form of CEA, outcomes aggregated into a unit of utility, e.g., quality-adjusted life-years (QALYs)
- Cost benefit analysis (CBA): costs weighed against outcomes aggregated into monetary units. Cost benefit analysis depends on assigning monetary values to the costs of interventions as well as the outcomes.

A basic example of a cost effectiveness calculation, to yield an ICER in the form of a cost per life-saved, is shown below.

\[
CE \text{ Ratio} = \frac{\$Cost_B - \$Cost_A}{Effect_B - Effect_A}
\]

For example:

<table>
<thead>
<tr>
<th></th>
<th>Total $ per 100 pts</th>
<th>Lives saved (LS) per 100 pts</th>
<th>Average CE Ratio</th>
<th>Incremental CE Ratio (ICER)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug A</td>
<td>1,000</td>
<td>8</td>
<td>$125/LS</td>
<td>8</td>
</tr>
<tr>
<td>Drug B</td>
<td>1,000,000</td>
<td>10</td>
<td>$100,000/LS</td>
<td>$489,500/LS</td>
</tr>
</tbody>
</table>

A basic cost utility analysis, which is a form of cost effectiveness analysis that uses a measure of patient utility such as a quality-adjusted life-year (QALY) is shown below.

\[
CU \text{ Ratio} = \frac{\$Cost_Y - \$Cost_X}{QALY_Y - QALY_X}
\]

For example:

<table>
<thead>
<tr>
<th></th>
<th>Total $ per patient</th>
<th>Life years per patient</th>
<th>Utility*</th>
<th>QALYs</th>
<th>Cost/QALY gained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug X</td>
<td>5,000</td>
<td>5.0</td>
<td>0.5</td>
<td>2.5</td>
<td>$107,000</td>
</tr>
<tr>
<td>Drug Y</td>
<td>250,000</td>
<td>6.0</td>
<td>0.8</td>
<td>4.8</td>
<td>$107,000</td>
</tr>
</tbody>
</table>

*Patient utility for remaining life years, ranging from 0=death to 1.0=perfect health
A useful concept for understanding the concept of cost-effectiveness is the cost effectiveness plane. This can be understood in four quadrants, which depend on the differences in costs and the differences in outcomes between a technology and its comparator, as shown below. The CEP plane demonstrates that any interventions that fall in either quadrant II or IV do not need ICERs to be calculated as they are either more effective and less costly (II), or more expensive and less effective (IV). Interventions falling in quadrant II are typically accepted, while those falling in quadrant IV are typically rejected. Since interventions in quadrant I are more effective but more costly, and those in quadrant III are less effective but less costly, ICERs need to be calculated and compared.

HTA has increasingly included budget impact analysis in recent years, particularly to provide a distinctive perspective of “affordability” to complement cost effectiveness analysis in support of decision making. Indeed, allocating resources efficiently (e.g., maximizing cost-effectiveness) may not be consistent with affordability, i.e., remaining within a particular budget.

Cost Measurement
Some key attributes to examine quality of cost measurement are: perspective for measuring cost; direct costs (health care and non-health care); indirect costs (e.g., loss of productivity); data capture method; time horizon of analysis; discounting of costs and outcomes over time.

Cost Utility Analysis Using Cost per QALY

QALYs are often used in cost-utility analysis for the purposes of optimizing allocation of health care spending to maximize QALYs gained, and thereby maximize social welfare. Cost per QALY gained, i.e., the marginal (additional or incremental) cost required to gain 1.0 QALY by using a technology (a type of ICER), is one way to quantify the value to society of using that technology instead of the standard of care or other alternative. Because the QALY incorporates length of life and quality of life but is not specific to any particular disease state or condition, it enables cost-utility comparisons across a wide spectrum of health care interventions.

Certain cost-per-QALY-gained levels have been cited as formal or informal decision “thresholds” for coverage of new interventions (e.g., the equivalent of approximately US$50,000, or US$100,000, or US$150,000 per QALY in the wealthy nations). There is increasing interest in using such thresholds in low- and middle-income countries, where the thresholds are adjusted downward for national wealth, sometimes as a function of gross domestic product (GDP) per capita. Comparisons of the cost per QALY gained from various health care interventions in widespread use can be revealing about how efficient health care systems are in allocating their resources.

Evidence Sources for HTA

The field of HTA has made great advances in methods for systematically searching literature to assemble the evidence base for conducting HTA. In planning for what types of literature should be searched, some considerations might be whether the following should be included any particular languages; grey literature; and data sets, registries, or information about ongoing clinical trials.

Depending on the purpose, scope, and target audience of an HTA, the potential sources of evidence and related information for an HTA could include any of: Bibliographic databases, study registries, scanning reference lists, queries to authors, searching for grey literature and so on. Among the bibliographic databases used most often in HTA are:

- PubMed (including MEDLINE)
- EmBase
- Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials)
- INAHTA Health Technology Assessment Database
- CINAHL
- PsycINFO

**Horizon Scanning**

In HTA, horizon scanning refers to ongoing tracking of multiple information sources to identify potential topics for HTA and provide input for setting priorities. Horizon scanning reports can provide rapidly completed, brief descriptions of new/emerging technologies and their potential impacts. While horizon scanning usually is used to identify new technologies that eventually may be topics for assessment, it can also involve identifying technologies that may be outmoded or superseded by newer ones. Horizon scanning can be used to:

- Identify technologies that have potentially major implications for health care
- Manage adoption and use of new technologies
- Identify areas of technological change
- Identify inappropriately used (including under- and over-used) technologies
- Enable health care providers, payers to plan for, adapt to technological change
- Plan data collection to monitor adoption, use, and impacts

**Priority setting in HTA**

Given the many technologies that could be assessed in HTA, it is necessary to set priorities. Horizon scanning can help to identify candidate technologies for assessment. Most HTA programs establish criteria and processes for selecting technologies for assessment. Examples of such criteria include:

- High individual burden of morbidity/mortality
- Large number of patients affected
- High individual or population cost of disease
- High unit or aggregate cost of technology
- Substantial variations in practice
- Unexpected adverse event reports
- Available findings not well disseminated or adopted by practitioners
- Sufficient research findings available upon which to base assessment
- Recent or impending regulatory approval
- HTA findings likely to have impact on clinical practice or coverage policy
- Public or political interest/pressure
Bibliographic sources and suggested readings


Research Protocol Writing in HTA

Authors: Maike Rehrmann, Alric Ruether
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 be analysed and summarised

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\(^1\) 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

1. Kick-off with assessment team
2. Collection of background information
3. Determination of research questions (e.g., PICO)

Stakeholder input (e.g., patients, external experts)

4. Writing the research plan
5. Research Protocol (1st draft)
   - Key sections of a research protocol:
     - Research questions
     - Search strategy
     - Study selection
     - Data extraction
     - Quality assessment
     - Data synthesis
     - Conflict of interests

6. Review of the protocol by independent reviewers
7. Revision

8. Final research protocol
9. Publication and public consultation, if applicable
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)

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

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

<table>
<thead>
<tr>
<th>Question</th>
<th>Aspects</th>
</tr>
</thead>
<tbody>
<tr>
<td>How does the technology work?</td>
<td>Drug or medical device, technical characteristics</td>
</tr>
<tr>
<td>What are the prerequisites of an application?</td>
<td>Prerequisite for application, qualifications, maintenance</td>
</tr>
<tr>
<td>What is the status of the technology?</td>
<td>Marketing, Degree of use, Fields of application, Current regulations, Manufacturers, Benefits and costs</td>
</tr>
</tbody>
</table>
Moreover, the research question should identify, inter alia, the 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:

**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.

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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,
Research Protocol Writing in HTA

- 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