KEMENKES RI

GENERAL GUIDELINE
FOR HEALTH TECHNOLOGY ASSESSMENT IN INDONESIA

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ORGANIZING TEAM

Directors

Prof. Dr. dr. Budi Wiweko Sp. OG (K) MPH
(Chairman of the Indonesian Health Technology Assessment Committee);
dr. Yuli Farianti, M.Epid
(Director of the Center for Health Financing and Decentralization Policy)

Organizing Team Members

Prof. Dr. Sri Suryawati, Apt (Team Leader),
Prof. drg. Mardiati Nadjib, MSc;
Prof. Budi Hidayat, SKM, MPPM, PhD;
Prof. Dr. dr. Ari Fahrial Syam, Sp.PD, KGEH FINASIM;
Prof. Dr. Purwantyastuti, MSc, Sp.FK;
Prof. Dr. dra. Erna Kristin, Apt, MSi;
dr. Jarir At Thobari, Ph.D;
drg. Armansyah, MPPM;
dr. Panji Fortuna Hadisoemarto, MPH;
drg. Lusiana Siti Masytoh, MKM;
dr. Resi Natalia Turnip, MKM;
Windi Haryani, SE, MKM;
dr. Eva Herlinawaty;
Miftahussaadah, SKM, MPH;
Ranti Dewi, SKM, MPH;
Nelly Mustika Sari, SKM, MKM;
dr. Tita Rosita, MKM.,
dr. Farida Trihartini, MKM;
dr. Dani Ramdani Budiman;
dr. Karlina;
Fraschiska Rizky Restuningtyas, S.Stat;
Mega Puspitasari, SE, Mec;
dr. Jannatiah.

INDONESIAN HEALTH TECHNOLOGY ASSESSMENT COMMITTEE
THE CENTER FOR HEALTH FINANCING AND DECENTRALIZATION POLICY
HEALTH POLICY AGENCY
MINISTRY OF HEALTH
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Organizing Team: Prof. Dr. Sri Suryawati, Apt; Prof. drg. Mardiati Nadjib, MSc;Prof. Budi Hidayat, SKM, MPPM, PhD;Prof. Dr. dr. Ari Fahrial Syam, Sp.PD, KGEH FINASIM; Prof. Dr.Purwantyastuti, MSc, Sp.FK;Prof. Dr. dra. Erna Kristin, Apt, Msi; dr. Jarir At Thobari, Ph.D; drg. Armansyah, MPPM; dr. Panji Fortuna Hadisoemarto, MPH; drg. Lusiana Siti Masytoh, MKM; dr. Resi Natalia Turnip, MKM; Windi Haryani, SE, MKM;dr. Eva Herlinawaty; Miftahussaadah, SKM, MPH; Ranti Dewi, SKM, MPH;Nelly Mustika Sari, SKM, MKM;dr. Tita Rosita, MKM., dr. Farida Trihartini, MKM; dr. Dani Ramdani Budiman; dr. Karlina;Fraschiska Rizky Restuningtyas, S.Stat; Mega Puspitasari, SE, Mec;dr. Jannatiah.
Editor Team : Prof. Dr. dr. Budi Wiweko Sp. OG (K) MPH, Prof. Dr. Sri Suryawati, Apt.

Directors:
Chairman of Indonesian Health Technology Assessment Committee
Director of Center for Health Financing and Decentralization Policy

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ACER	Average Cost-Effectiveness Ratio
BIA	Budget Impact Analysis
BPJS	Badan Penyelenggara Jaminan Sosial (Social Security Administrator)
BPOM	Badan Pengawas Obat dan Makanan (National Agency of Drug and Food Control)
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CBA	Cost-Benefit Analysis
CEA	Cost-Effectiveness Analysis
CMA	Cost-Minimization Analysis
CUA	Cost-Utility Analysis
DALY	Disability-Adjusted Life Years
DSA	Deterministic Sensitivity Analysis
GDP	Gross Domestic Product
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
INA CBGs	Indonesia Case-Based Groups
JKN	Jaminan Kesehatan Nasional (National Health Insurance)
MRI	Magnetic Resonance Imaging
NIE	Nomor Izin Edar (Distribution Permit Number)
OS	Overall Survival
PFS	Progression-Free Survival
PICO	Population Intervention Comparator Outcome
PSA	Probabilistic Sensitivity Analysis
PTK	Penilaian Teknologi Kesehatan (Health Technology Assessment)
QALY	Quality-Adjusted Life Years
RCT	Randomized Controlled Trial/ Randomized Clinical Trial
RWD	Real-World Data
RWE	Real-World Evidence
SR	Systematic Review
WTP	Willingness-to-Pay

GREETINGS FROM THE DIRECTOR OF THE CENTER FOR HEALTH FINANCING AND DECENTRALIZATION POLICY

Health Technology Assessment (HTA) is an effort to control the quality and cost of the National Health Insurance or Jaminan Kesehatan Nasional (JKN) program, as mandated in Presidential Regulation Number 82 of 2018 on Health Insurance. Health Technology Assessment in National Health Insurance program. HTA is conducted to assess the effectiveness and efficiency of the use of technology or technological products in the form of methods, medicines, or medical devices in health services so that it becomes one of the ideal tools in reviewing benefit packages in the JKN program. HTA has been implemented since 2014 and is currently entering its eighth year. Since the formulation of this guideline, 14 recommendations have been produced and will continue to grow in the coming year.

In accordance with its authority, the Indonesian HTA (InaHTA) Committee's duties are conducting health technology assessments and providing policy recommendations to the Minister of Health based on the HTA results. The Center for Health Financing and Decentralization Policy [formerly known as the Center for Financing and Health Insurance], is a part of the Ministry of Health which acts as the InaHTA Commitee Secretariat and can also serve as an HTA agent that fully supports the InaHTA Committee and the HTA implementation to be well-conducted.

HTA implementation refers to guidelines that control the course of the study. The previous guidelines are governed by the Ministry of Health Regulation number 51 of 2017 on Health Technology Assessment Guidelines in the National Health Insurance program. Along with the rapid development of science and health technology in medicines, medical devices, and new procedures, these guidelines need to be revised.

In terms of health policy, the government wants to ensure that the health technology used by the community in the JKN program is up-to-date and effective, evidence-based medicine, prioritizing patient safety, with the proper funding allocation. On the payer side, the results of a well-implemented HTA study are expected to have an impact on expenditure efficiency and control of service costs.

This guideline is a reference in conducting HTA for the Ministry of Health, HTA Committee, HTA agents, and other related stakeholders such as professional organizations, Social Security Administrator for Health, health care facilities association, academics, pharmaceuticals, various units in the Ministry of Health, and for HTA enthusiasts and observers in Indonesia.

We want to thank all stakeholders who have paid attention and contributed to the preparation process of these guidelines. We realize that in the formulation of this guideline, there are still shortcomings, and we really appreciate your input for the improvement in the next edition. May Allah the Almighty always give His grace and guidance to all of us. Aamiin.

Jakarta, September 2022

Director of the Center for Health Financing and Decentralization Policy

dr. Yuli Farianti, M.Epid

GREETINGS FROM THE CHAIRMAN OF HEALTH TECHNOLOGY ASSESSMENT COMMITTEE

The Indonesian Health Technology Committee (InaHTA Committee) was established to conduct studies and provide health policy recommendations to the Minister of Health based on the results of health technology assessments both clinically and economically. The assessment involves multidisciplinary disciplines covering safety, efficacy, effectiveness, social, economic, organizational or legal, and ethical aspects. It can even include cultural and religious aspects.

In the implementation of HTA, evaluation of various aspects of a new or pre-existing health technology is conducted by gathering and synthesizing evidence on its effectiveness, cost, and impact on the patient's quality of life. Currently, the need for HTA is increasing along with the increasing number of inputs from professional associations, pharmaceuticals, and health facilities. It indicates that the need for the adoption of health technology in Indonesia is quite high. Therefore, HTA guidelines are needed as a reference for quality and standardized HTA implementation to support transparent and evidence-based decision-making in health technology policy. The process starts with selecting priority topics, assessing, appraising, and preparing HTA policy recommendation notes.

Revisions in this guide include improving and focusing methods and applications related to topic selection using multiple-criteria decision analysis (MCDA), adopting the adaptive HTA (aHTA) method, and real-world data (RWD) or real-world evidence (RWE). It is hoped that the revisions to these guidelines will support the HTA implementation that is timely, reliable, consistent, and relevant to the policymakers' requirements. It is our great hope that these guidelines can provide

optimal benefits for various stakeholders involved in HTA studies, especially the InaHTA Committee, the Ministry of Health, HTA agents, and other relevant stakeholders. As a closing remark, we express our appreciation and deepest gratitude to all members of the HTA Committee, the Director of the Center for Health Financing and Decentralization Policy, the World Bank, and the USAID Medicines, Technologies, and Pharmaceutical Services (MTaPS) Program, and the Department of Foreign Affairs and Trade (DFAT) Australia for their support in the development of this guideline.

Jakarta, September 2022

Chairman of Indonesian Health Technology Assessment Committee

Prof. Dr. dr. Budi Wiweko Sp. OG (K) MPH

EXECUTIVE SUMMARY

Chapter 1 - Introduction

- The Health Technology Assessment (HTA) is a multidisciplinary process that assesses the technical, safety, efficacy, effectiveness, and broader social aspects of the use of health technologies.
- The health technologies that can be a topic of HTA includes medicines, medical devices, surgical or non-surgical medical procedures, and public health programs.
- In order to control the quality and cost of the National Health Insurance implementation, HTA in Indonesia is conducted by the HTA Committee following the applicable laws and regulations.
- Questions related to policies that can be answered by the HTA Committee, in particular regarding the implementation of the JKN program, include but are not limited to, whether a health technology can be listed in, delisted from, or used with restrictions within JKN, or as a basis for price negotiation.

Chapter 2 – Indonesian Health Technology Assessment Committee

- The InaHTA Committee is established by the Minister of Health and independently provides recommendations regarding health technology to the Minister of Health based on the HTA results.
- In conducting its duties, InaHTA Committee is aided by the Secretariat Team, HTA Agents, Expert Panels, and Ad hoc Panels.
- Chapter 3 – Stakeholders and HTA Agents in Indonesia
- All individuals, organizations, or communities who have an interest in and/or are involved in the HTA process and/or are affected by the HTA results are HTA stakeholders.
- InaHTA Committee identifies and invites all relevant stakeholders to participate in the HTA process.

- HTA Agents refer to institutions or organizational entities that are assigned to conduct the health technology assessment.
- The Ministry of Health, universities, research institutes, and hospitals can act as HTA agents in Indonesia.

Chapter 4 – HTA Implementation Mechanism in Indonesia

- HTA implementation in Indonesia consists of six steps, namely: 1) topic selection, 2) assessment by HTA Agents, 3) appraisal, 4) preparation of policy recommendations, 5) submission of policy recommendations, and 6) publication of HTA results.
- Topic selection is conducted in five steps, namely 1) gathering topic proposals, 2) verifying the completeness of topic proposal documents, 3) preparing topic priorities, 4) determining HTA topic priorities, and 5) disseminating the decision of HTA topic priorities.
- InaHTA Committee gathers the topic proposals both passively and actively. Passive topic gathering is conducted periodically, and each stakeholder can submit their proposal by completing specified forms and documents. Active topic gathering is conducted through HTA Committee's independent studies or consultations with experts.
- The InaHTA Committee prioritizes topics based on volume, technological impact on health, cost, concordance with the government's policy priorities, potential cost savings, and public acceptance of the proposed health technology.
- Health technology assessment is conducted by HTA agents from the Ministry of Health, universities, research institutions, and hospitals. The team consists of multidisciplinary researchers, in consultation with the InaHTA Committee and the Expert Panel. In conducting the assessment, agents can collaborate with other agents or parties.
- Health technology assessment is conducted by following these steps: 1) establishing HTA assessment team, 2) preparing a pre-proposal, 3) preparing the proposal and

research instruments, 4) obtaining permits for data collection, 5) collecting and analyzing data, 6) compiling and writing reports on the assessment results, and 7) submitting the final report on the assessment results to the Indonesian HTA Committee's Secretariat Team.

- The expert panel consists of experts representing professional organizations, academics, and experts in relevant fields.
- HTA study or assessment questions are written explicitly by explaining the target population, the technology or intervention being assessed, the comparator, and the outcomes to be measured.
- The assessment report is written according to the CHEERS consensus.
- The InaHTA Committee appraises the following: 1) results of HTA studies conducted by HTA agents and 2) other aspects of the health technology not assessed in the ongoing assessment process.
- In conducting the appraisal, the InaHTA Committee is assisted by an independent ad hoc panel.
- In the appraisal meeting, the InaHTA Committee and the ad hoc panel conduct health technology assessments on the following aspects: a) assessment methodology, b) clinical effectiveness, c) cost effectiveness, d) cost-utility per year of life, e) budget impact, f) social, g) cultural, h) political, i) ethical, j) religious, k) equity, and l) affordability.
- The InaHTA Committee makes decisions on related health technology to answer the proposed policy questions. These decisions may take the form of but are not limited to, listing, delisting, price negotiations, or health technology restrictions. The steps in decision-making are: 1) formulation of interim decisions, 2) dissemination, 3) final decision-making, and 4) preparation of the final HTA report and InaHTA Committee's recommendation notes.
- Interim decisions are formulated in the plenary meeting of the InaHTA Committee. The interim decisions are disseminated

to relevant stakeholders and they can respond to or refute the decision within 30 days.

- The HTA Committee makes a final decision by considering and, if necessary, following up on stakeholder responses or objections to be subsequently formulated as a recommendation note from the InaHTA Committee to the Minister of Health.
- The HTA summary that has been completed is published through publicly accessible media platforms.

Chapter 5 – Economic Evaluation Method in the Health Technology Assessment Process

- Economic evaluation in HTA refers to the following criteria:
  1. The type of economic evaluation conducted is Cost-Utility Analysis (CUA) and the outcome is measured in the form of Quality-Adjusted Life Years (QALY).
  2. The evaluation takes on a societal perspective.
  3. A target population is a population group in Indonesia that becomes the target of health technology interventions following the HTA topic. Subpopulation analysis can be conducted as needed.
  4. The analyzed interventions are interventions or health technology that has been determined as the HTA topic. Clinical evidence related to the intervention is reviewed through systematic review and meta-analysis. The real-world data can describe the local context and complement the results of systematic review and meta-analysis.
  5. The selected comparators are standard-of-care interventions or usual care interventions in clinical practice.
  6. The outcome used is Quality-Adjusted Life Years (QALY), which is measured by EQ-5D-5L instruments from EuroQol Group with an Indonesian value set.
  7. The time horizon used should be long enough to cover all

relevant cost consequences and intervention output.

8. Costs are calculated from the societal perspective, including direct medical costs, direct non-medical costs, and indirect costs.
9. Discounting is applied to clinical outcome and costs using a discount rate of 3%.
10. Economic evaluation analysis is conducted using decision tree analysis or Markov model as needed.
11. Sensitivity analyses must be conducted using deterministic and probabilistic methods.

- The cost-effectiveness of health technology is assessed by comparing the incremental cost-effectiveness ratio with the value of Indonesia's GDP per capita, which acts as a threshold value. Specific threshold value for Indonesia can be used if it is available.
- Budget Impact Analysis (BIA) should always be conducted in conjunction with an economic evaluation. It is seen from the payer's perspective, for a 5-year time horizon, by only calculating the direct medical costs. Discounting is not applied in the BIA calculation.
- HTA implementation can be adapted to limited resources, data, and time, through the implementation of adaptive HTA (aHTA).

CHAPTER 1

INTRODUCTION

Chapter 1
Introduction

Health technology assessment or HTA (henceforth will be called as HTA) is a multidisciplinary process that employs explicit methods to determine the value of health technology at a specified time in its utilization cycle. In assessing a health technology, clinical, epidemiological, statistical, economic, social, cultural, ethical, political, and religious aspects are also considered. HTA results are used as scientific information that is objective, actual, factual, and evidence-based in the decision-making process to realize an impartial, efficient, and quality health system.

HTA can be applied on health technology used in the fields of medicine and public health, such as those used for promotive, preventive, curative, and rehabilitative purposes. Thus, what is meant by health technology as the HTA subject includes medicine and biological products (e.g., vaccines), medical procedures, both surgical and non-surgical, medical devices, to programs implemented in the public health sector (e.g., cancer screening).

- Medicines are substances or a combination of substances, including chemical or biological products, which are used to influence or investigate physiological systems or pathological conditions in the context of establishing a diagnosis, prevention, treatment, recovery, health promotion, and contraception for humans.
- Medical devices are instruments, apparatuses, machines, and implants that are used to prevent, diagnose, heal, and alleviate disease, treat the sick, restore health in humans, form structures, and improve bodily functions. Medical devices produce their primary effects, not through chemical reactions within or on the surface of the body.
- Medical procedures are a series of activities performed on a patient for the purpose of improving health status, treating illness or injury, and making a diagnosis.
- Public health programs are organized public health activities,

which can include health services, community mobilization, research, evaluation, surveillance, and policy development.

It is quite clear that the definitions of various types of health technology that can become the HTA object are not mutually exclusive (for example, a public health program may involve a medical procedure that uses one or more medicines and medical devices). Therefore, in HTA implementation, it is important to provide clear boundaries regarding health technology that becomes the HTA object and policy questions that will be answered by the HTA.

When this revised guideline was formulated, the implementation of HTA in Indonesia was mandated by Presidential Regulation Number 82/2018 on Health Insurance as one of the tools for quality and cost control in the implementation of the national health insurance program. Presidential Regulation Number 82/2018 also specifies the types of technology that are included as the HTA objects, namely "procedures, medicines, or medical devices [used] in health services in the health insurance program". In the context of JKN implementation, HTA is conducted to answer policy questions: whether a health technology is eligible to be listed, delisted, price negotiated, or restricted in its use in the benefits package of the health insurance program. In addition, the HTA results can be used to answer other policy questions, such as in the context of medicines registration, formulation of National Guidelines for Medical Services, and Clinical Practice Guidelines.

HTA as a scientific method can also be used for various stakeholders' objectives, and they can conduct HTA for different purposes (e.g., it is in the hospital's interest to conduct HTA to decide whether or not to buy a medical device). The objectives and policy questions that need to be answered in an HTA must be stated explicitly.

HTA is a scientific process that involves various disciplines. The aspects assessed in HTA are as follows:

- Safety. The safety of health technology use can be obtained from direct observation, routine reports from hospitals, case reports in the literature, or side effect reports obtained from clinical

trials. It should be noted that clinical trials usually include only a few thousand or even a few hundred subjects. Thus, rare, and fatal side effects may be difficult to document from clinical trials alone. These rare side effects may be documented through meta-analysis or phase IV clinical trials (postmarketing surveillance).

- Technical characteristics. Technical characteristics, especially for medical devices both for diagnostic (e.g., MRI, CT-scan, hybrid angiocardiography) and therapeutic purposes (e.g., stent, hearing aids), are of importance. Manufacturers and service providers expect the proper functioning of this health technology; hence proper maintenance needs to always be implemented. In health technology, it really needs to be considered whether the specifications, indications for use, maintenance, and calibration have been done according to manufacturer's requirements.
- Efficacy. The efficacy of a medicine or clinical procedure is best assessed through randomized controlled trials (RCTs) with carefully selected subjects so that their characteristics are homogeneous. Clinical trials like these have good internal validity but poor external validity due to differences in subjects' characteristics from the general patients. Therefore, its application in practice needs to be done with caution.
- Effectiveness. Health technology effectiveness is also best assessed through RCT. In contrast to efficacy studies, the selection of subjects in clinical trials that assess the effectiveness of a health technology is not conducted with very strict criteria as in efficacy studies. Subjects' selection is designed so that their characteristics are similar to patients in daily practice. While maintaining good internal validity, these studies also have good external validity so that the results can be applied in the patient's daily management.
- Social, legal, ethical, political, and religious impacts. Some social, legal, ethical, political, and religious aspects can be evaluated by literature review. However, it must be interpreted using social, cultural, legal, and ethical perspectives in the local context. Religious aspect of the Indonesian people needs special attention because the majority of Indonesia's population is Muslim. The involvement of experts in this field is required.

- Economic evaluation. Economic evaluation can elaborate whether a health technology has value for money. It is an indicator that shows the expenditure on a health technology is proportionate with the impact it produces.
- Budget impact. Budget impact analysis is conducted to see the budget consequences such as the potential adjustment in expenditure that would be experienced if the intervention were borne by the payer.

This guideline elaborates the implementation of health technology assessments for the aspects of clinical effectiveness, economic evaluation, and budget impact analysis, written in a separate chapter for use by HTA agents or other stakeholders who will conduct health technology assessments.

This revised guideline also opens opportunities for the use of new methods in HTA, such as adaptive HTA (aHTA) and the use of real-world data and evidence. Those new methods and its technical implementation will be provided in a separate document. Regardless of the current drawbacks, it is hoped that this guideline will be able to meet the requirements of HTA implementation in Indonesia, particularly in the context of JKN implementation, by the InaHTA Committee, HTA agents, and HTA stakeholders.

CHAPTER 2

INDONESIAN HEALTH TECHNOLOGY ASSESSMENT COMMITTEE

Chapter 2
Indonesian Health Technology Assessment Committee

In the framework of implementing HTA to support the health insurance program, the Minister of Health establishes the Indonesian Health Technology Assessment Committee (InaHTA Committee), which is stipulated through a Minister of Health Decree. It consists of individuals deemed to have relevant skills, experience, and positions for the implementation of HTA in Indonesia. Although this committee is structured under the Minister of Health, the InaHTA Committee will independently make its own decisions. InaHTA Committee's decisions, related to the utilization of a health technology, are formulated based on the assessment and appraisal results, written in the form of recommendation notes.

The InaHTA Committee is led by a chairman who is assisted by members of the InaHTA Committee and the Secretariat Team while performing their duties.

2.1 Indonesian Health Technology Assessment Committee (InaHTA Committee)

In general, InaHTA Committee's duty is to conduct systematic and objective assessments of various health technologies' utilization impacts and provide recommendations based on the HTA results to the Minister of Health. With the Health Insurance Program in mind, the InaHTA Committee's recommendations may include but are not limited to, listing, or delisting a health technology from a benefit package. It may also recommend restrictions on indications for the use of a technology that is already included in the benefit package. InaHTA Committee can also recommend an acceptable price limit for the health technology to be included or kept in the benefit package (negotiation).

In the HTA process, a list of topics or health technologies, decided on by the InaHTA Committee, will be prioritized. Then, the HTA agents, appointed by the InaHTA Committee,will perform the economic evaluation assessment for the selected topics. In addition, the InaHTA Committee has established a panel consisting of representatives of

professional organizations and experts who are relevant to the selected topic.

Once a decision based on the result of the health technology assessment has been made by the InaHTA Committee it will be disseminated to stakeholders to open up the opportunities for input and objections regarding said decision. The InaHTA Committee is then responsible for the follow up of inputs and/or objections received, which in turn will be considered in the making of the final decision. The final decisions are conveyed in the form of a policy recommendation note to the Minister of Health. The completed HTA summary is then published through publicly accessible media platforms. Although, the implementation of the recommendation notes is not the responsibility of the InaHTA Committee (only relevant institutions), the committee is still required to monitor the implementation of these recommendations.

In general, the InaHTA Committee's responsibilities are as follows:

1. Determining priority topics to be assessed by health technology assessment (HTA). If necessary, the process may involve relevant institutions and experts to provide input;
2. Appointing HTA agents to conduct the health technology assessments, establishing an expert panel consisting of professional organization representatives and experts relevant to selected HTA topics, and providing assistance and evaluation of the assessment process;
3. Performing an appraisal of the assessment results, assisted by an ad hoc panel;
4. Formulating policy recommendation notes to be submitted to the Minister of Health;
5. Developing HTA institutions in Indonesia;
6. Periodically reviewing HTA guidelines;
7. Developing activity plans and evaluating HTA activities;
8. Constructing and strengthening the Indonesian HTA network both domestically and internationally.

2.2 Secretariat Team

The Secretariat Team is led by the Secretary to coordinate, both the technical and administrative aspects of HTA. In general, the Secretariat

Team's responsibilities are as follows:

1. Coordinate the process of selecting and announcing HTA priority topics;
2. Coordinate the appointment of the HTA team, supervise the implementation of HTA, perform the HTA appraisal, the objection period, and the completion process;
3. Coordinate HTA activities in preparing and submitting HTA policy recommendation notes;
4. Coordinate the preparation of technical policies for the HTA implementation, advocacy, and dissemination of HTA policies;
5. Coordinate with the InaHTA Committee and other relevant stakeholders in supporting HTA activities;
6. Perform administrative coordination and report HTA activities.

The duties and responsibilities of the InaHTA Committee and the Secretariat Team are regulated more specifically in the stipulating legislation that determines the panelship of the InaHTA Committee.

CHAPTER 3

HTA STAKEHOLDERS AND AGENTS IN INDONESIA

Chapter 3
HTA Stakeholders and Agents in Indonesia

3.1 HTA Stakeholders

The involvement of many stakeholders during the HTA implementation and production of policy recommendations, if implemented, will certainly impact certain stakeholders. All individuals, organizations, or communities who have an interest in and/or are involved in the HTA process and/or are affected by the HTA results are considered HTA stakeholders in Indonesia. These stakeholders may include, but are not limited to:

1. Government agencies or public legal entities, such as the Ministry of Health, the Health Office, and the Social Security Administrator for Health (BPJS Kesehatan).
2. Producers and commercial industries, including companies that produce medicines and medical devices.
3. For-profit and not-for-profit organizations providing public and private health services, including clinic associations and hospital associations.
4. Organizations that represent practitioners, such as health practitioners or professionals whose practices are affected by the HTA processes and outcomes, or professional organizations that can influence the implementation of policy recommendations (e.g., medical professional associations),
5. Organizations that finance and conduct research, such as donors, universities, or research institutions based in Indonesia.
6. Organizations that use health services or technology, or the general public, such as patient organizations or health care non-profit organizations.
7. International agencies operating in Indonesia or whose policies are influential in Indonesia, such as the World Health Organization, the World Bank or other relevant development partners.

The involvement of stakeholders can guarantee that decisions are made based on an accountable HTA. In contrast to the expert's

consultation process, stakeholders involved in the HTA process are permitted to offer unsolicited feedback without being requested by the InaHTA Committee. Involving the stakeholders, the InaHTA Committee adheres to the following principles.

- Transparency. All information must be open and honest for all stakeholders.
- Inclusivity. HTA implementation must provide equal access to opportunities and resources for all stakeholders.
- Impartiality. Processes and decisions of the HTA Committee are not influenced by personal or particular group interests.
- Commitment. In all HTA stages, all stakeholders are ready to engage in a two-way conversation.
- Accessibility. Given the multidisciplinary process, the outputs of the HTA must be accessible and understandable to all relevant stakeholders involved.
- Accountability. Accountable reporting comes after the two way dialogue and input processes between the InaHTA Committee and stakeholders..
- Responsiveness. Stakeholder comments and opinions are welcome during the full InaHTA Committee decision making process.
- Willingness-to-learn. The InaHTA Committee and stakeholders in the HTA process, which incorporates numerous scientific disciplines and evolving methodologies, are always receptive to new information in order to provide high-quality HTA outcomes.

The stakeholders are involved through the following stages:

1. Depending on the kinds of technology and health issues that constitute the HTA priority, the InaHTA Committee determines the stakeholders who need to be involved. For instance, whether the medical specialization, patient population, or service provider is connected to the technology or health problem.
2. Following the identification of the stakeholders, the InaHTA Committee contacts and officially invites all stakeholders to take part in relevant HTA processes. This stage describes the HTA

process that will be conducted, the HTA's goals, the potential impact of the policy, and what is anticipated from the involvement of the relevant stakeholders. The InaHTA Committee can also invite stakeholders via public announcement platforms, such as websites or social media.

3. In accordance with the commitments agreed between the InaHTA Committee and the stakeholders, the InaHTA Committee involves ready stakeholders to participate in one or more of the following activities
    - Collecting information and suggestions about the health technology to be assessed,
    - Participation entails actively involving stakeholders at all stages and incorporating them into all processes. It includes facilitating the collection of data needed during the assessment.
    - Consultation, to obtain feedback on specific findings.

On each stage of HTA mechanism, stakeholders are involved based on their respective roles, such as:

1. Topic selection stage

    InaHTA Committee involves various stakeholders to propose HTA topics that will be studied on. Professional organizations, hospitals, the pharmaceutical industry, various units in the Ministry of Health, and the Social Security Administrator for Health (BPJS Kesehatan) are examples of stakeholders that can be involved on this stage.

2. Assessment stage

    At this stage, HTA agents and an expert panel are determined. Professional organizations with an interest on the subject may nominate individuals to be included in the expert panel. Furthermore, HTA agents will develop protocols and conduct assessments under the supervision of the InaHTA Committee and expert panel.

3. Appraisal stage

    The InaHTA Committee appoints professional organizations and

relevant experts to allocate their members who are not actively involved in the assessment process as an ad hoc panel for the appraisal stage.

4. Preparation of recommendations stage

   Decisions based on the assessment and appraisal results are then disseminated by the InaHTA Committee to all stakeholders involved, such as professional organizations, experts panel, hospitals, universities, various units in the Ministry of Health, National Agency of Drug and Food Control (BPOM), Social Security Administrator for Health (BPJS Kesehatan), and the pharmaceutical industry. According to their respective disciplines, these stakeholders are given the opportunity to provide comments and objections to the InaHTA Committee's interim decisions.

Stakeholders' involvement provides an opportunity for the InaHTA Committee to better understand the issues at hand and also provides stakeholders a better understanding of the HTA process in Indonesia. Their involvement at all stages of HTA is needed to ensure that relevant and important issues are taken into account during HTA implementation, in order to make decisions or formulating recommendations. Therefore, the policies created through HTA are transparent, relevant, accountable, and excellent.

3.2 HTA Agents

In Indonesia, HTA agents can include the Ministry of Health, universities, research institutions, and hospitals. HTA agents are those assigned by the InaHTA Committee to perform the assessment process.

In order to become an HTA agent, an institution must have qualified personnel and a track record of conducting adequate HTA studies. A multidisciplinary research team is needed for the HTA process that include pharmacoeconomists, modeling experts, epidemiologists, health economists, and other experts.

CHAPTER 4

HTA IMPLEMENTATION MECHANISM IN INDONESIA

Chapter 4
HTA Implementation Mechanism in Indonesia

This chapter provides an overview of the stages conducted by the InaHTA Committee in implementing HTA in Indonesia. It focuses on the context of implementing the National Health Insurance (JKN) program. A general description of each stage is provided, and if necessary, a more detailed explanation will be supplied in a separate document.

In general, the HTA process consists of six stages. The first stage is topic selection, which is followed by an assessment process, an appraisal, and the formulation of policy recommendations to be submitted to the Minister of Health. Every HTA assessment and recommendation that passes the appraisal stage is published by the InaHTA Committee so that it can be accessed by the public (Figure 4.1).

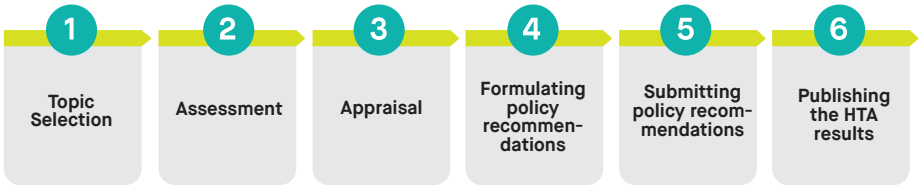

Figure 4.1 The implementation mechanism of health technology assessment

4.1 Topic selection

HTA activities begin with topic selection in health technology. This stage involves transparent, thorough, structured, and scientific processes for determining priority topics for HTA implementation. Stages in determining the priority topic are presented in Figure 4.2.

Figure 4.2. The selection flow of health technology assessment topics

1. Topic collection

   Topic collection for health technology assessment is conducted actively or inactively by the InaHTA Committee. HTA topics are passively collected by the InaHTA Committee based on suggestions from various stakeholders, such as professional associations, hospitals, BPJS Kesehatan, patient associations, universities, pharmaceutical or medical device industries, independent research institutes, and various units at the Ministry of Health. Periodically, stakeholders are given the opportunity to propose HTA topics, and the InaHTA Committee Secretariat will notify them of this opportunity via official letters and publicly accessible media such as websites or social media. In addition, the InaHTA Committee can also actively propose HTA topics based on its own studies or consultations with experts.

   In order to submit HTA topics, the proposer must complete and submit an online topic proposal form (Appendix 1) accompanied by supporting documents and data in the form of:

   1. Information, data, explanations, and supporting documents related to the proposed health technology and its competitor;
   2. Published and unpublished scientific journals (grey literature) that discuss the safety, efficacy, effectiveness, and quality of the health technology;
   3. Costs and utilities, including data on incidence, prevalence, and disease burden;
   4. Other relevant supporting data.

Health technology that can be proposed as an HTA topic includes medicines, medical devices, and medical procedures, both surgical and non-surgical. In general, health technology can become the subject of an HTA study if it is a new technology that has proven its safety and effectiveness. It has the opportunity to improve patients' health, national programs, and policies but has not been used in health services or guaranteed in a benefits package. Meanwhile, the health technology that is currently in use or has been included in the benefit packages can also become an HTA topic if the aspects of safety, efficacy, effectiveness, or economic implications are deemed necessary to be reviewed.

Off-label use of medicines that have been registered in BPOM can be considered to become an HTA topic if:

a. off-label use of medicines is in line with good international practice and, taking into account the standard of care for the population proposed in local practice,
b. it is life-saving, or other medical options are not yet available for the condition in question,
c. there is sufficient evidence to assess the safety, clinical effectiveness, and cost-effectiveness aspects.

Medicines that are not yet registered in Indonesia (do not yet have a Distribution Permit Number (NIE) can be considered as HTA topics if:

a. it is life-saving or other medical options are not yet available for the condition in question,
b. there is sufficient evidence to assess the safety, clinical effectiveness, and cost-effectiveness aspects.

The positive results of HTA studies on off-label medicine indications and medicines that do not yet have a distribution permit number (Nomor Izin Edar/NIE) do not eliminate the pharmaceutical industry's obligation to perform the registration process.

2. Verification of the entirety of topic proposal documents

   InaHTA Committee Secretariat verifies the completeness of

incoming proposals using the available checklist (Appendix 1). If necessary, the InaHTA Committee Secretariat can communicate with the proposer to clarify the proposal and request additional documents.

3. Prioritization of topics

   After the proposal submission period is closed, the InaHTA Committee holds a plenary meeting to sort all incoming and verified topics by conducting an assessment based on the following criteria (Figure 4.3):

   - Volume. It refers to the amount of health technology is used, either as a percentage of service used in the health insurance program or as a percentage of estimated disease burden.
   - Technological impact on health. It includes a positive impact from technological efficacy or effectiveness to reduce the disease burden, improve quality of life, and reduce negative impacts due to medication adverse effects or its inappropriate use
   - Cost. It is the unit cost of applying technology or the price that must be paid to complete one cycle of treatment, screening, or action. Proposers must pay attention to the variability of costs and prices in various types and places of health services.
   - Concordance to prioritized government policies.
   - The potential cost savings that can be achieved if the technology is used.
   - Public acceptance. It includes public concern towards the technology from social, cultural, ethical, political, and religious perspectives.

Figure 4.3. The criteria used by the HTA Committee in the process of prioritizing HTA topics.

The scoring system of this assessment mechanism for each of the above criteria will be described in a separate document from this general guideline.

4. Determining HTA priority topics

   InaHTA Committee determines the priority topics for HTA implementation based on the scoring results in Stage 3 above. The topic with the highest score will get the highest priority to be assessed. The number of topics that will be assessed varies each year.

5. InaHTA Committee informs the public and the proposer regarding the priority of HTA topics that has been determined through publicly accessible medias.

4.2 Assessment

The Health Technology Assessment is a scientific process that produces evidence sourced from various literature and local data in Indonesia. The process of HTA involves multi-stakeholders and multi-professionals.

In summary, the HTA assessment stages are described in Figure 4.4.

Figure 4.4. The assessment flow of health technology assessment

The steps in the HTA implementation can be explained as follows:

1. Establishing a health technology assessment team. The health technology assessment team (HTA team) consists of HTA agents accompanied by supervisors from the InaHTA Committee and a panel of experts. Health technology assessment is conducted by HTA agents from the Ministry of Health, universities, research institutions, and hospitals in consultation with the InaHTA Committee and the expert panel. In conducting the assessment, agents can collaborate with other agents or stakeholders such as the Ministry of Health, universities, research institutions, and hospitals. The expert panel consists of experts with various scientific disciplines originating from professional organizations that are relevant to the HTA topic.
2. Preparing pre-proposal. The pre-proposal is a brief presentation document or material that contains an outline of the assessment protocol to be executed (Appendix 2). The pre-proposal is prepared by the technical team with the objective of obtaining clarification and information from the InaHTA Committee and the expert panel on various aspects needed in the preparation of a complete review proposal or protocol.
3. Formulating proposal and research instruments. Research proposals and instruments are prepared based on protocols that had been approved by the InaHTA Committee and the expert panel. The complete proposals are prepared according

to a predetermined format (Appendix 3). Research proposals must explicitly state HTA questions which will be answered following the PICO format below:

- Target population (Population = P)
- Technology or intervention (Intervention = I)
- Comparator (Comparator = C)
- The expected output will be achieved with the application of this health technology (Outcome = O)

With clear protocols covering focused research questions, researchers have clear references to set definitive and directed objectives as a basis for conducting the studies. A literature review can help researchers formulate research questions. More specific questions, secondary questions, and questions at a subgroup level can also be developed as needed. The HTA agents must also ensure that the formulated research questions are relevant to the broader policy questions that have been determined by the InaHTA Committee for the HTA topic in question. The preparation of HTA study proposals and protocols by HTA agents is described in Chapter 5 of this guidebook.

4. Submitting data collection permits for HTA. Ethics and permits are part of the procedure to ensure patient safety and data confidentiality. The procedure for submitting ethical clearance and data collection permits conforms to the procedures applied at the health facility or institution.
5. Data collection and analysis. The data collection process is conducted according to the requirements, and the data analysis is conducted following the assessment proposal that has been prepared. HTA agents regularly consult with the expert panel and InaHTA Committee in the process of data collection and analysis.
6. Preparing and writing the report of assessment results. The assessment reports are written following the rules of scientific writing and a predetermined checklist (Appendix 4). At the time this guide was written, the convention was the CHEERS consensus published in 2022. The more recent

consensus can be used if the consensus is revised in the future. The checklist listed in Appendix 4 (or a later checklist, if any) is included as an appendix to the final report.

7. Submitting the report of assessment results. The report and its supporting documents (executive summary, presentation material, checklist, raw data, assessment analysis model, and a statement letter from the HTA team on the report's approval) are submitted to the InaHTA Committee Secretariat to be appraised by the InaHTA Committee. After all submitted documents are declared complete, the InaHTA Committee Secretariat will submit and schedule an appraisal for the InaHTA Committee.

4.3 Health technology appraisal

After the final assessment report is received by the InaHTA Committee from the HTA agent, the appraisal is performed by the InaHTA Committee along with an ad hoc panel from professional organizations or related stakeholders. The appraisal process consists of two main agendas, namely 1) appraisal of the HTA results conducted by HTA agents and 2) appraisal of other aspects of health technology that are important HTA topics in answering policy questions but are not part of the ongoing assessment process. The latter is conducted by HTA agents, and the aspects appraised are social, cultural, equity, and other aspects. The appraisal processes include:

1. Establishing an ad hoc panel

   The InaHTA Committee appoints professional organizations and experts that are relevant to the HTA topic being assessed. The professional organization assigns its members to an ad hoc panel. Members of the ad hoc panel must meet the following requirements:
   a. They are not involved in the health technology assessment process, and they are not a member of the expert panel;
   b. They are committed to executing the entire appraisal process; and
   c. They must sign conflicts of interest statements.

2. Appraisal meeting

   The InaHTA Committee Secretariat sends the results of the health technology assessment and other supporting data to all members of the InaHTA Committee and members of the ad hoc panel no later than one week before the appraisal meeting.

   The appraisal process is conducted in an appraisal meeting attended by the InaHTA Committee, the ad hoc panel, the InaHTA Committee Secretariat, and the HTA Team. A meeting is considered valid if it is attended by at least 50% plus one member of the InaHTA Committee and at least 2/3 of the members of the ad hoc panel. The appraisal meeting is chaired by the InaHTA Committee Chair or a designated member. Under certain conditions, InaHTA Committee members from the Ministry of Health can be represented by appointed staff.

   In this process, the InaHTA Committee and the ad hoc panel assess a) assessment methodology, b) clinical effectiveness, c) cost effectiveness, d) cost-utility per year of life, e) budgetary impact, f) social, g) cultural, h) political, i) ethical, j) religious, k) equity, and l) affordability aspects. The technical details of each aspect of the appraisal process above will be explained in a separate document from this general guideline.

   The appraisal decision is written in an official report and signed by the InaHTA Committee and the ad hoc panel. The HTA Team is given time to respond or follow up on decisions of revisions (if any) no later than ten working days.

4.4. Formulation of recommendation notes

The formulation of the HTA policy recommendation notes is conducted by considering the principles of transparency, accountability, and participation. The InaHTA Committee formulates policy recommendations in the form of policy recommendation notes based on policy questions proposed on the HTA topic assessment. InaHTA Committee recommendations can be in the form of listing, delisting, price negotiation, and restriction on health technologies for their utilization in certain programs, and so on, especially within

the scope of the JKN program. In this decision-making process, the InaHTA Committee may involve relevant stakeholders. The formulation of recommendation notes is conducted in four stages, which are briefly presented in Figure 4.5.

Figure 4.5. The decision-making process of health technology assessment

1. Formulating an interim policy recommendation note.

   After the appraisal process is conducted, the InaHTA Committee holds a plenary meeting attended by all of its members to prepare an interim recommendation note with reference to the discussions, conclusions, and recommendations written in the minutes of the appraisal.

   Every decision is urged to be taken on the basis of deliberation to reach a consensus. In the event that a consensus cannot be reached, a decision can be made based on the majority vote, provided that all members of the InaHTA Committee cast their votes. Decisions supported by at least 50% + 1 person from all members of the InaHTA Committee are determined as interim decisions. Dissenting opinions of InaHTA Committee members on recommendation points, if any, are written in a separate report.

2. Disseminating the HTA results that have been appraised by the InaHTA Committee and the interim recommendation notes.

   Interim policy recommendations are conveyed through dissemination activities by inviting all relevant stakeholders. The HTA Committee will submit the assessment results and interim policy recommendations.

3. Period for rebuttals and hearings.

   After the interim decision has been announced to the public, stakeholders can submit responses or rebuttals to the interim decision within 30 calendar days since the decision was announced in the dissemination forum. Responses or rebuttals are sent along with a letter of introduction by email to the InaHTA Committee Secretariat. The InaHTA Committee will respond if there are objections from stakeholders through hearings. This hearing is attended by the InaHTA Committee, objectors, and the InaHTA Committee Secretariat in order to obtain clarifications or objections with supporting evidence.

4. Ratification of HTA policy recommendation notes

   Following the resolution of all objections, the InaHTA committee will hold one plenary meeting to ratify the final recommendations as outlined in the final policy recommendation note.

4.5. Submission of the InaHTA Committee's recommendation notes to the Minister of Health

The InaHTA Committee submits the HTA policy recommendation note to the Minister of Health in order for it to be considered as a possible policy in the health insurance program or other policies as needed.

4.6. Publication of HTA results

As a part of public information disclosure, the InaHTA Committee, via the HTA Secretariat, publishes a summary of HTA results through publicly accessible media platforms, such as websites and press releases. Conflicts of interest statements from each stakeholder involved in the HTA process, if any, must also be made public.

CHAPTER 5

ECONOMIC EVALUATION METHOD IN THE HEALTH TECHNOLOGY ASSESSMENT PROCESS

Chapter 5

Economic Evaluation Method in the Health Technology Assessment Process

Economic evaluation is an important component of HTA, the process is performed by HTA agents in the assessment stage. To obtain consistent, transparent, and systematic results, InaHTA Committee appoints reference-case as a guideline for HTA agents in conducting HTA and helping stakeholders evaluate the assessment results' validity.

Reference criteria are the preferences and consensus of the InaHTA Committee regarding the methods and assumptions of a health technology assessment, which may differ from the preferences or consensus underlying the reference criteria in other countries. In general, health technology assessments that do not follow the reference criteria are not used by the InaHTA Committee as a basis for policy recommendations. However, certain topics that require analysis and assumptions that do not follow the reference criteria (non-reference cases) are still permitted with justification and approval from the InaHTA Committee and the expert panel at the ratification stage of the HTA proposal. HTA can be conducted for various health technologies such as medicines (including biological products and vaccines), medical devices, medical or surgical procedures, and health technologies used in public health programs. The reference criteria described in this chapter are intended as guidelines for implementing the economic evaluation of health technology, particularly but not limited to health technology in the form of medicines. These referral criteria apply to non-medicine health technology in general. Although the assumptions and analysis of the non-medicine economic evaluation may differ from the reference criteria, the decision to implement a non-reference case assessment must be reviewed case by case. The components of the HTA reference criteria in Indonesia can be seen in Table 5.1.

Table 5.1 Summary of the HTA reference criteria in Indonesia.

Component	Reference criteria	Subchapter
Types of economic evaluation	Cost-utility analysis (CUA) in incremental cost-effectiveness ratio (ICER)	5.1
Perspective	Societal	5.2
Population (P)	The patient population in Indonesia	5.3
Intervention (I)	Health intervention that becomes the HTA topic	5.4
Comparator (C)	Standard of care and usual care	5.5
Outcome (O)	Quality-adjusted life years (QALY)	5.6
Time horizon (T)	Long enough to cover all relevant outputs	5.7
Cost	Direct medical costs, direct nonmedical costs, and indirect costs.	5.8
Discount	3% for health costs and outcome	5.9
Approach	Modeling	5.10
Sensitivity analysis	Must be conducted	5.11
Results interpretation	Using GDP per capita as the threshold value: < 1x GDP per capita – very cost-effective; 1-3x GDP per capita – cost-effective. Until threshold values specific to the Indonesian context are determined..	5.12

5.1 Types of economic evaluation

There are several types of economic evaluation that can be conducted in HTA, namely cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-benefit analysis (CBA), and cost-minimization analysis (CMA), which are selected based on differences in clinical effectiveness and units of measurement for health outcomes. The reference criterion for health technology assessment in Indonesia is cost-utility analysis.

Cost-effectiveness analysis (CEA)

CEA is an economic evaluation with health outcomes expressed in natural units (e.g., mortality, morbidity). CEA allows the comparison of two or more health interventions that provide health outcomes that can be measured in the same natural units but have different magnitudes.

Cost-utility analysis (CUA)

Cost-utility analysis is a special form of CEA with health outcomes expressed as the quality of life that patients obtain after receiving health technology interventions. Quality of life indicators are developed from the concept of utility and are calculated in the form of quality-adjusted life-years (QALYs) or disability-adjusted life-years (DALYs). The outcomes that become the reference criteria for HTA in Indonesia are QALYs. Further explanation can be seen in the output subsection of this chapter.

Cost-benefit analysis (CBA)

CBA or cost-benefit analysis is used to compare two or more health technologies that are used for different purposes and produce outcomes that have different natural units. In order to compare these interventions, the cost and output components are measured in monetary value (Rupiah) the amount of which is adjusted according to the calculation period (discounted).

Cost-minimization analysis (CMA)

CMA is used to compare two or more health technologies that provide the same, similar, or equivalent clinical outcomes. Because the impact of two or more of these interventions on the outcome is (considered to be) the same, hence only one intervention will be compared, which is costs.

The final result of CUA used in the HTA reference criteria is the incremental cost-effectiveness ratio (ICER), which shows the difference in cost ratio (C) between the new intervention (C_1) and the comparator (C_0) to the difference in effect (E) between the new intervention (E_1) and comparator (E_0):

$$ICER = \frac{(C_1 - C_o)}{(E_1 - E_0)}$$

The ICER value is compared to a threshold value to assess whether the intervention has "value for money". The average cost-effectiveness ratio (ACER), which shows the average cost for each unit of effect obtained (i.e., C/E), is not used as an HTA reference criterion in Indonesia.

5.2 Perspective

The perspective taken from the HTA economic evaluation determines the relevant health outcomes and costs to be considered. The three alternative perspectives that can be taken include the payer, health system, and social perspectives. The perspective taken as the HTA reference criterion in Indonesia is a societal perspective that considers the broad social impacts of decision making based on the HTA results that are not limited to individuals receiving the analyzed technological interventions or the health sectors.

5.3 Population and subpopulation

The patient population, or target population that is subjected to the health technology intervention (HTA topic), is the Indonesian population group, with clear and specific inclusion and exclusion criteria. The target population must be described based on age, sex, socio-economic status, type of disease or comorbidities, and other relevant characteristics. If data is collected from a sample, the data collection method, including sample size and sample selection, must be explained, and justified so that the sample characteristics represent the target population or patients' characteristics. Subpopulation analysis related to heterogeneity in the target population can be performed as needed, for example, if there is a large variation in the outcomes among the relevant subpopulations.

5.4 Intervention

The analyzed interventions are interventions or health technologies that have been determined as the HTA topic. As part of the health

technology assessment, the HTA agents must conduct a review of existing clinical evidence regarding the safety, efficacy, and clinical effectiveness of the assessed health technology. The modeling to be conducted in the analysis will also require quality evidence related to clinical parameters, underlying baseline risks of a clinical condition, prevalence or incidence data, use of resources, cost, quality of life, and diagnostic test accuracy. The relevance of evidence is important for a decision model in an economic evaluation process and can be assessed based on the hierarchy or level of evidence available for the questions to be answered (Table 5.2).

Table 5.2 Evidence hierarchy for questions related to a health problem or intervention. Level 1 is the highest level of evidence.

Questions	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem found?	Current and local random sample survey (or via census)	A systematic review of various surveys that are relevant to local conditions**	Non-randomized local sample**	Case series**	n/a
Is the diagnostic examination or monitoring accurate? (Diagnosis)	A systematic review of cross-sectional studies with consistent blinding and reference	Individual cross-sectional studies with consistent blinding and reference standards	Non-consecutive studies, or studies without consistent reference standards**	Case-control studies or studies with poor or non-independent reference standards**	Mechanism-based reasoning
What will happen if no treatment is given? (Prognosis)	A systematic review of the initial cohort study	Initial cohort study	Cohort study or randomized control arm clinical trial	Case series or case-control studies, or prognostic cohort studies of poor quality**	n/a
Will the applied intervention have an impact? (Management advantages)	A systematic review of the randomized test or n-of-1 trial	RCT or observational study with dramatic effect	Non-randomized controlled cohort or follow-up study**	Case series, case-control study, or historically-controlled study**	Mechanism-based reasoning

Questions	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
What are the common disadvantages? (Management disadvantages)	A systematic review of RCTs, systematic review of nested case-control studies, n-of-1 trials with associated patients, or observational studies with dramatic effect	Individual RCT or observational study with dramatic effect	Non-randomized controlled cohort or follow-up studies (post-marketing monitoring) allow numbers found to exclude common losses. (For long-term losses, follow-up duration should be sufficient)**	Case series, case-control study, or historically-controlled study**	Mechanism-based reasoning
What are the uncommon disadvantages? (Management disadvantages)	A systematic review of RCT or n-of-1 trial	RCT or observational study with dramatic effect			
Is early detection beneficial to be performed? (Screening)	Systematic review of RCT	Randomized test	Non-randomized controlled cohort or follow-up study**	Case series, case-control study, or historically-controlled study**	Mechanism-based reasoning

(Source: "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653)

*The level may be lowered based on baseline study quality, imprecision, indirectness (the PICO study did not match the PICO question), because there is inconsistencies between studies, or because there presence of a very small absolute effect; The level may be increased if there is presence of a large or very large effect.

** In general, a systematic review is assessed better than individual study

Systematic review and meta-analysis

A systematic review (SR) and meta-analysis have an important role in reviewing clinical evidence. SR is a process of reviewing the evidence with clearly formulated questions and using systematic and explicit methods to identify, select, appraise, extract, and analyze data from relevant studies. SR implementation can refer to the steps described in the applicable international SR guidelines (for example Cochrane Handbook for Systematic Reviews of Interventions). In general, the steps in SR can be summarized as follows:

1. Determine the purpose of a systematic review.
2. Develop review protocols, including defining questions, inclusion and exclusion criteria, search strategies, methods and designs in study selection, data extraction and relevant software, instruments for quality assessment, and data synthesis methods. The PICO criteria can be used to determine review questions and literature searches.
    a. Population: it can be a population with a health condition, stage of a disease, risk factors
    b. Intervention: health technology or equivalent, health intervention, medicine (dose / frequency / regimen), diagnostic examination (mode / frequency), health policy
    c. Comparator: it depends on the research questions, standard care, or routine care
    d. Outcomes: mortality, morbidity, quality of life
3. Do a comprehensive search with specific keywords. The use of Boolean operators (OR, AND, NOT) is recommended in the electronic search. Database selection for electronic search depends on accessibility, the topic scope, and data type.
4. Eligibility of the study is determined according to the inclusion and exclusion criteria set a priori. PRISMA flow diagrams are usually used to determine this.
5. Perform data extraction on specific characteristics of the studies involved, adjust to the questions, and review protocol. Information on the PICO elements involved.
6. Appraise evidence quality by using standardized assessment instruments.
7. Synthesize data involving collation, combination, and summary of findings from studies that are part of SR. Pooling of these findings can be done statistically or narratively.

Meta-analysis is an analysis of a set of individual research that has been analyzed. It aims to integrate the findings in individual research. To perform a meta-analysis of interventional studies, standard outcome measurement data from the involved studies are needed. For example, the results of individual studies with binary outcomes

will be reported as the effect measurement in the form of an odds ratio or risk ratio. In a meta-analysis, diagnostic accuracy, sensitivity, specificity, and likelihood ratio will be the primary outcomes.

Because the sample sizes in each individual study are not the same, in order to combine several studies, appropriate statistical methods must be used. The most commonly used statistical techniques are the fixed effect model and the random effect model. In general, the fixed effect model is used if the combined studies are homogeneous. Sometimes both methods are used to show that the results of the two methods are not much different. The results of the meta-analysis are reported narratively and are always complemented by a forest plot.

In each meta-analysis, researchers must be aware of publication bias. Researchers generally tend to submit the results of the study for publication if the results are positive (statistically significant), while journal editors also tend to accept articles with significant results. Studies with insignificant results are more often submitted to local or national journals, while studies with significant results are published in international journals. With the presence of publication bias, global literature will be dominated by studies whose results are statistically significant.

Real-world data and real-world evidence

Clinical effectiveness data are usually obtained from RCTs or SR from RCT studies. Although RCTs have good internal validity, allowing causal inference and relative effectiveness assessments to be made with a high degree of confidence, their external validity is limited because the subjects usually have different characteristics from the general patient population. Therefore, real-world data (RWD) is defined as data obtained from contexts other than RCTs that can describe the local context (Table 5.3). Meanwhile, real-world evidence (RWE), the results of RWD analysis, are often needed to assess the effects of health technology (including safety, effectiveness, resource usage, etc.) in the context of local health services. The use of RWD and RWE in health technology assessment will be described in detail in a separate document from this general guideline.

Table 5.3 RWD primary and secondary sources

RWD primary source	RWD secondary source
• The patient register is collected prospectively • Non-experimental studies • Pragmatic randomized clinical trial • Patient or provider survey	• Retrospective data from patient register or database • Medical records, both electronic and analog • Claim data • Service and cost data on the hospital information system (SIRS) • Laboratory data

5.5 Comparator

The comparators selected, as reference criteria, are standard of care or usual care interventions in clinical practice. Standard of care is the first-choice intervention based on applicable clinical guidelines, whereas usual care is a routinely given intervention to the health condition being studied and may not be the standard of care. The comparator selection must follow the clinical context of the case under study, be clearly described, and be complemented by a strong justification as to why the comparator is more relevant than the others.

5.6 Outcome

The outcome used in the CUA analysis for the HTA reference criteria in Indonesia is Quality-Adjusted Life Years (QALYs). The QALYs used as the HTA reference criteria in Indonesia are measured using the EQ-5D-5L instrument from the EuroQol Group with an Indonesian value set (Purba et al., 2017). The measurement is conducted by combining the effects of health technology on the life expectancy with changes in quality of life as a result of interventions using this technology. QALY measurement allows the comparison of two medical technologies used for different purposes (e.g., cardiovascular and cancer medicines).

Other outcomes that can be measured as the effect of an intervention using a health technology are not used as reference criteria but can be referred, if a justification is provided. For example, the

effect of an intervention can be measured by intermediate clinical outcomes (e.g., the percentage of biomarker levels, the number of deaths prevented, etc.), or final outcomes measured in terms of overall survival (OS) or progression-free survival (PFS). Final clinical outcomes are obtained from systematic reviews and meta-analyses (or equivalents).

5.7 Time horizon

The time horizon applied in the analysis must be long enough to capture accurately all the cost consequences and outcomes of the interventions. The same time horizon should be applied to output and costs.

5.8 Cost

Costs are calculated from a social perspective so that they include all relevant cost components, namely direct medical, and nonmedical costs, as well as opportunity costs which are calculated in Rupiah. Identification and calculation of costs must be conducted in a transparent and systematic manner using primary data. Ideally, the sources and samples of cost data represent the variation that exists in Indonesia. Thus, the justification for the selection and limitations of the sample must be explained. In calculating costs, researchers must ensure the calculations' accuracy and avoid underestimation or double counting.

Direct medical costs

Direct medical costs are costs incurred directly to provide medical care, whether paid by insurance or out-of-pocket. Data sources that can be used are secondary data from health facilities billing, INA-CBGs rates, or other relevant data sources.

Direct nonmedical costs

Direct nonmedical costs are costs incurred by patients and their families that are directly related to the treatment efforts but are not medical in nature. Examples of direct nonmedical costs are the cost of transporting patients to healthcare facilities, the cost of meals, and patients' accommodation during treatment. The data source that can be used is patient interviews.

Indirect costs

Indirect costs are costs issued due to loss of productivity because of illness or death. Data sources that can be used are patient or guardian interviews. An example of indirect cost for a patient is loss of income from leave or workdays lost due to illness, permanent disability, or premature death. An example of an indirect cost for companions is loss of income as a result of not working due to time spent accompanying the sick.

5.9 Discounting

Discounting is a method used to adjust the current costs and outcomes with their values in the future. Discounting must be applied to both outcomes and cost values if the analysis' time horizon exceeds one year. The discount rate used as the reference criterion is 3% for the cost and outcome values.

5.10 Analysis techniques

Economic evaluation analysis of a health technology can be conducted empirically (for example: using data collected in the implementation of clinical trials) or using a model-based approach. The economic evaluation used as a reference criterion for HTA in Indonesia is a model-based economic evaluation. Commonly used models are decision trees, the Markov model, or the dynamic model for infectious diseases. The modeling selection must be adjusted to the context in which HTA is implemented, including the type of intervention and the health or disease condition being studied. The model used should be as simple as possible but should reflect real-world clinical practice so that the involvement of clinical experts will be necessary. The use of models that are more complex is permitted but must be justified. Parameters used in the modeling must be obtained from good quality sources and relevant to the target population. In the report, the limitations and assumptions of the model are presented transparently.

5.11 Sensitivity analysis

Economic evaluations are always followed by uncertainties. A sensitivity analysis should be performed to quantify the uncertainties

surrounding the estimates of costs, outcomes, and ICER due to the uncertainties surrounding the model parameters. The need to extrapolate results to a certain time or from an intermediate to a final outcome also causes uncertainties about the results of studies that may be performed in a relatively short period of time. As a reference criterion, sensitivity analysis is conducted either deterministically or probabilistically. Deterministic sensitivity analysis (DSA) is conducted using one-way sensitivity analysis, which is displayed in a tornado diagram. Probabilistic sensitivity analysis (PSA) is conducted using Monte Carlo simulation and presented as cost-effectiveness acceptability curve and a cost-effectiveness plane.

5.12 Result interpretation

In determining whether a health technology is cost-effective or not, it is assessed by comparing the incremental cost-effectiveness ratio (ICER) with Indonesia's GDP per capita, which acts as a threshold value. A health technology with an ICER of less than or equal to GDP per capita is considered very cost-effective, while technology with a ratio between 1-3 times the value of GDP per capita is considered cost-effective. If these values are available, decision-making can be made using the threshold values calculated specifically for the Indonesian context.

5.13 Budget Impact Analysis (BIA)

BIA is not an economic evaluation but is an integral part of the economic evaluation results of an intervention or health technology (HTA topic). BIA must be conducted as an estimate of the financial consequences in the form of expenses or cost savings from the adoption of health technology, especially in the health insurance program package. BIA requires additional data to estimate coverage, such as prevalence, incidence, population size, and costs from the payer's perspective. The differences between BIA and Cost-Effectiveness Analysis are as follows:

Table 5.4 Differences between BIA and CEA in decision-making

Type of analysis	The studied population	Time horizon	The example of measured outcomes	Value for decision-makers
CEA	Yearly or individual incidence cohort data according to the cases studied	According to the time horizon of the studied disease	Incremental life years, Incremental QALY Cost, or QALY gained	Decision on the selected intervention that is dominant compared to the comparator (has "value for money" compared to the threshold)
BIA	The entire population or estimated number of populations suffering from the disease	Annually, calculated for the next five years	Changes in service fees every year for the next five years, changes in mortality or morbidity every year according to the BIA calculation period	• Budget planning • Achievement of output targets (programs or interventions)

The analysis basically includes the cost calculations of the interventions studied. It estimates the difference between service costs using the currently available interventions and their impact on increasing the budget, and finally conducts a sensitivity analysis. The components analyzed will determine the required data, namely:

1. Cost. All expenditure estimates and savings must be related to the overall impact of health services at the national level. In simpler terms, BIA is performed to present the impact of medicine procurement costs. More extensively, the impact of costs can cover the overall impact of health service costs that occur as a result of interventions or new technologies that are introduced.
2. Discount is not applied because the BIA is intended to explain the implications of additional funding or the additional budget requirement as a consequence of the decision to choose a new benefit package.

3. Health condition and population target. The population's health condition and the current treatment pattern must be explained comprehensively and in detail. It is related to the intervention towards the studied health problem. The estimated target population, or potential access to the studied intervention, includes all patient populations who are eligible to receive the intervention at a given time period. Therefore, not only incidence but also prevalence data are needed. The justification is that patients who previously had access to the disease treatment (using existing medicines or interventions) will have the opportunity to seek out and obtain new interventions or medicines. This is known as "induced demand" and has implications for the new medicine's market expansion. In addition, an increase in demand can also occur because there is a growing number of sick people.
4. The interventions and their comparator are introduced.. The safety, efficacy, effectiveness, and side effects of new health technologies must be explained and compared to existing interventions or medicines. The comparator must be described, and its comparison will impact the new intervention proposal. This impact will be reflected in several analyzed factors, such as the incidence rate of the disease treated by the medicine or intervention studied, its diagnosis and treatment, resources, and costs.
5. Time horizon. The time horizon is measured every five years as a base case, and the annual flow of the required budget consequences is mandatory based on realistic implementation scenarios.

The BIA is calculated using the criteria listed in Table 5.4. BIA results are reported along with the economic evaluation results.

Table 5.5 Criteria used in budget impact analysis

Component	Reference criteria
Perspective	Payer
Population (P)	The patient population in Indonesia
Intervention (I)	Health technology that becomes the HTA topic
Comparator (C)	Standard of care and usual care
Time horizon (T)	Five years
Cost	Direct medical cost
Discount	Is not conducted
Analysis techniques	Modeling, considering the realistic implementation process
Sensitivity analysis	Must be conducted (in the form of alternative scenarios)

5.14 Adaptive health technology assessment (aHTA)

The HTA implementation follows the reference case with the mechanism described above may be handicapped by limited resources, data, and time. Under these conditions, one or more HTA components can be modified to adjust to the existing limitations. This pragmatic approach is known as adaptive HTA, or aHTA. Although this term has not been used consistently for the intended HTA approach (another term, for example, is rapid HTA). The aHTA method is highly contextual and a relatively new approach, so at the time this guideline was developed, there was no consensus on best practices or gold standards. The inclusion of aHTA in this guideline is intended to accommodate its implementation if there are conditions that justify the implementation of aHTA.

aHTA is made possible by "transferring" epidemiological or clinical data, economic evaluations, models, and decisions taken or published in other countries,considering their transferability and other uncertainties. In addition, aHTA includes a simplification of the standard HTA mechanism to shorten the HTA implementation time (Table 5.5). Since aHTA is very flexible, the aHTA objects are similar to the normal HTA in terms of the scope of policy questions and the types of health technology used. However, the feasibility of the proposed aHTA method must be assessed case by case and

decided by the InaHTA Committee before it can be used as a basis for recommendations or decision-making. Adaptive HTA implementation instructions will be written in a separate document from this general guideline.

Table 5.6 The comparison of traditional HTA and adaptive HTA (adapted from Nemzof et al., 2021)

	Normal HTA	Adaptive HTA
Project duration	6 months or more	Less than 6 months
Topic selection	Following the standard topic selection mechanism	Opportunistic or using the simplified mechanism or using modified selection criteria
Assessment	De novo economic evaluation, collection of high-quality primary data or UKR, and systematic review or meta-analysis	Economic evaluations are adapted from other countries, price benchmarking, literature reviews, and data from easily accessible sources or rapid reviews.
Appraisal	Follows the standard appraisal mechanism	Follows a simplified appraisal mechanism
Decision-making	Decision-making is based on traditional HTA results	Decision-making is based on adaptive HTA results or HTA results in other countries

5.15 Reporting

Reports are presented systematically, completely, and transparently. The reporting component refers to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) issued by ISPOR (Appendix 5). These standards are updated regularly, and researchers are advised to use the most recent standards when preparing the reports.

CHAPTER 6

CLOSING REMARKS

Chapter 6
Closing Remarks

This revised guidebook for HTA studies in Indonesia has been formulated to accommodate recent developments in HTA methods, especially in the implementation of economic evaluations and possible future changes in the HTA requirement in Indonesia. On the other hand, several HTA methods are also rapidly developing , so this general guideline needs to be supplemented with much detailed technical instructions and is easily adapted to scientific developments and requirements. Adaptive HTA, for example, is an HTA method that has begun to be widely used to meet the HTA requirements in the context of conducting HTA studies amid limited resources, such as data availability or time. However, there is no consensus or examples of best practices in the implementation of adaptive HTA.

The need to use RWD and RWE is also becoming increasingly important, considering various data limitations coming from RCTs or health services contexts that are different from the policy-making context in Indonesia. On the other hand, the quality of the data from routine services in Indonesia is often inadequate to produce a high quality RWE, which leads to invalid HTA conclusions. The analysis used to produce RWE from RWD is also very diverse and must be selected based on valid scientific judgments. This guideline places RWD and RWE as valid sources of information to be used in HTA studies, but it needs to be elaborated in a separate technical guideline. Thus, they are more specific but flexible enough to keep up with the scientific developments and requirements in HTA implementation.

This guideline also accommodates the possibility of HTA for non-medicine health technology, included in public health programs. When this guideline was compiled, the InaHTA Committee held the mandate to conduct HTA as a means to control the quality and cost of the health insurance program's implementation. Therefore, in the context of current policy requirements, the ongoing HTA topics focused more on medicines that were already in the national health

insurance benefit packages. However, HTA as a scientific method is not limited solely by the need to implement a health insurance program. In addition, the mandate given to the HTA Committee in the future may change. In many cases, the reference criteria written in this general guideline can be used for non-medicine HTA, although there will be exceptions in practice.

In the end, quality HTA can only be obtained with the support of adequate and qualified resources. Universities and educational institutions have a very important role in encouraging the generation of competent human resources in conducting HTA. The HTA is required in health insurance implementation and also in the making of other policies, ranging from policies on equipment procurement at health service facilities to national policies in public health. As the need for HTA implementation will continue to increase, it should then be addressed as an opportunity to increase the volume of human resources in the HTA sector.

The InaHTA Committee hopes that the HTA agents and other stakeholders involved in the HTA process and results, are able to utilize this revised guideline to further improve the quality of HTA implementation in Indonesia. With great hopes that this guideline will serve as a reference and discussion material for researchers conducting future HTA studies in Indonesia. Encouraging the production of standardized and high quality HTA studies, which in turn can help create an impartial and of high quality health system in Indonesia.

APPENDIX

Appendix 1. The structure of HTA proposal submission form

The structure of HTA proposal submission form

Categories	Objectives	Questions/Instructions
Cover letter issued by the proposing institution	To obtain an official document from the institution that proposed the topic	Attach cover letter with letterhead and/or official stamp (if any)
Data of Proposer 1	To obtain the identity of the main proposer that proposes health technology – which is submitted as the topic of the Health Technology Assessment	Fill in the name, institution, position, correspondence address, mobile number, email
Data of Proposer 2	Same as above - optional	
Proposed Health Technology	To obtain the type of proposed health technology	Choose the type of proposed health technology
Proposed Health Technology – Medicines / Medical Devices / Health Procedures / Other Technologies	To obtain brief information on the type of proposed health technology	Fill in the name of the proposed medicine, the distribution permit number, attach the distribution permit, the indications mentioned in the distribution permit, the proposed indication for health technology assessment, safety, or preparation (medicine), instructions for use (medical device), etc.
Comparator (Comparative Health Technology)	To obtain brief information from other health technologies that are a comparator for the proposed technology	
Justification for Topic Submission	To obtain a detailed explanation in the form of basis, evidence, and reasoning related to the proposed health technology	Prevalence / incident / utilization (volume), positive and negative impacts of the proposed technology on health, costs associated with the proposed technology, conformity with policy priorities, potential cost savings, acceptance of the proposed technology, additional information supporting the proposed topic, and etc.
Input for General Design Form	To obtain input for form improvements	Do you experience technical difficulties in filling out this form, do all questions include all the technological details that I want to submit, can all the required information be obtained easily.

Details of Topic Submission Completeness

1. Cover letter for proposal submission with official letterhead and/or stamp (if any) from the proposing institution/organization
2. Official certificate/permit/guide related to technology:
   a. The distribution permit number (NIE) for the proposed health technology (for example, for a proposed topic on medicines, it is accompanied by a distribution permit number from BPOM and for non-medicines or medical devices from the Directorate General of Pharmaceuticals and Health Medical Services, the Ministry of Health, or an authorized official), if any;
   b. Management guidelines related to the proposed health technology (example: PNPK, etc.).
   c. For medicines: attach a page of the National Formulary showing the registration of the proposed medicine.
   d. For medical devices: (1) a photo of the proposed medical device; (2) document instructions for the use of the proposed medical device.
3. Supporting documents related to the comparator of the proposed technology (for example: Distribution Permit Number, product photos, etc.), if any.
4. Information, data, description, and supporting documents related to the technology:
   a. The estimated unit cost of technology usage per illness episode or per patient, or per year of use;
   b. Incidence, prevalence, and disease burden data related to the proposed health technology (with sources).
   c. Utilization data or health technology usage claim data (with sources).
   d. Publication in scientific journals relevant to the proposed topic concerning the safety, efficacy, effectiveness, and quality of health technology.
   e. Unpublished documents (grey literature, if any) relevant to the proposed topic;
   f. Other relevant supporting data (e.g., technology-aligned policy documents).

Appendix 2. The Outline of Health Technology Assessment Pre-Proposal

The Assessment Title	:
Implementation Team	:
Date	:

1. Background
2. HTA Questions (policies and research)
3. Methodology:
    a. Population
    b. Intervention
    c. Comparator
    d. Output
        i. Clinical output
        ii. Nonclinical output
    e. Types of economic evaluation
    f. Perspective
    g. Time horizon
    h. Cost
    i. Discount
    j. Modeling analysis techniques
    k. Sensitivity analysis
    l. Budget Impact Analysis
    m. Primary data collection
4. Initial references summary
5. References
6. Timetable
7. Budget planning

Notes: Pre-proposal is formulated briefly (less than three pages)

Appendix 3. The Outline of Health Technology Assessment Proposal

The Outline of Health Technology Assessment Proposal

1. The title of health technology assessment
2. Researchers' name (can be more than one) and institution of origin
3. Chapter 1 Introduction consists of:
    a. Background
    b. Policy Questions
    c. Research Questions
    d. Objectives of the Study
    e. Significance of the Study
4. Chapter 2 Literature Review
5. Chapter 3 Methodology
    a. Clinical Effectiveness Method:
        i. Evidence searches strategies
        ii. Inclusion and exclusion criteria
        iii. Critical review
        iv. Data extraction
        v. Data synthesis
    b. Economic Evaluation Methods
        i. Types of economic evaluation
        ii. Perspective
        iii. Population and subpopulation
        iv. Intervention
        v. Output
        vi. Time horizon
        vii. Cost
        viii. Discounting
        ix. Analysis techniques
        x. Sensitivity analysis
        xi. Results interpretation
        xii. Budget Impact Analysis (BIA)
        xiii. Data collection processes
6. Time table
7. Budget planning
8. References
9. Appendices: Questionnaires or forms used in the study and other relevant documents to the assessment method that will be conducted.

Appendix 4. The Report Format of Health Technology Assessment Results

The Report Format of Health Technology Assessment Results

1. The title of health technology assessment
2. Researchers' name (can be more than one) and institution of origin
3. Executive Summary
   The executive summary is formulated comprehensively. The main objective is to provide sufficient information to the policymakers in order to obtain evidence-based information. The executive summary is presented in both Indonesian and English languange.
4. Systematic
   a. Chapter I Introduction
      1) Background of the Study
      2) Policy Questions
      3) HTA Research Questions
      4) Objectives
      5) Significance of the Study
   b. Chapter II Literature Review
   c. Chapter III Research Method
      1) Method Review
      2) Clinical Effectiveness
         a) Evidence-seeking strategies
         b) Inclusion and exclusion criteria
         c) Critical review
         d) Data extraction
         e) Data synthesis
      3) Economic Evaluation Methods:
         a) Design and model
         b) Parameter model
         c) Transitional probability of clinical effectiveness
         d) Cost variables, utility variables, and study perspectives
         e) Model analysis and time horizon
         f) Uncertainty analysis
         g) Budget Impact Analysis
   d. Chapter IV Research Organization

1) Data Collection Processes
2) Preparation Stage and Study Implementation

e. Chapter V Results
1) Clinical Effectiveness Evidence
2) Economic Evaluation
3) Budget Impact Analysis

f. Chapter VI Discussions
g. Chapter VII Conclusions and Recommendations

5. Funding Sources
6. Conflicts of Interest Statement
7. References
8. Appendices

Appendix 5. CHEERS 2022 Checklist

CHEERS 2022 Checklist

Section/Topic	No	Guidance for reporting	Reported in section
Title			
Title	1	Identify the study as an economic evaluation and specify the interventions being compared.	
Executive summary			
Abstract	2	Provide a structured summary related to context, key methods, results, and alternative analyses (500 words at maximum).	
Executive summary	3	The executive summary must be written no longer than three pages and is written in non-technical language. This section must include: a. Problems: statements about economic policies or issues or reasons for economic evaluation b. Method c. Results: contains a numerical and narrative summary d. Discussions: limitations of the study, relevance of findings, impact on health services e. Conclusion: evaluation findings, outcome uncertainties, and caveats	
Introduction			
Background and objectives	4	Describe the study overview, research questions, and relevant practices to policy decision-making.	
Method			
Health economic analysis plan	5	Indicate whether a health economic analysis plan was developed and in which section.	

Section/Topic	No	Guidance for reporting	Reported in section
Study population	6	Describe characteristics of the study population (such as age, range, demographics, socioeconomic, or clinical characteristics).	
Setting and location	7	Provide relevant contextual information that may influence findings.	
Comparator	8	Describe the interventions or strategies being compared and why it is chosen.	
Perspective	9	State the perspective(s) adopted by the study and why it is chosen.	
Time horizon	10	Describe the time horizon applied in the analysis.	
Discounting	11	Report the discount rate(s) and the reason why it is chosen.	
Output selection	12	Describe what outcomes were used as the measure(s) of benefit(s).	
The measurement of outcomes	13	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	
Valuation of outcomes	14	Describe the population and methods used to measure and evaluate outcomes.	
Measurement and valuation of resources and costs	15	Describe how costs were valued.	
Currency, price date, and conversion	16	Report the dates of the estimated quantities and unit costs, the exchange rate, and the year of conversion.	
Rationale and description of the model	17	If modeling is used, describe in detail and why it is used. Report if the model is publicly available and where it can be accessed.	

Section/Topic	No	Guidance for reporting	Reported in section
Analysis and assumption	18	Describe any analysis methods or statistically transforming data, any extrapolation methods, and approaches to validate any model used.	
Heterogeneity characterization	19	Describe any methods used for estimating how the results of the study vary for sub-groups.	
Distributional effects characterization	20	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	
Uncertainty characterization	21	Describe methods to characterize any sources of uncertainty in the analysis.	
Approach to patients and others affected by the study	22	Describe any approaches to engage patients, the general public, communities, or stakeholders (e.g., physicians or payers) in the study.	
Result			
Study parameters	23	Report all analytic inputs (e.g., values, ranges, references), including uncertainty or distributional assumptions.	
Summary of the results	24	Report the mean values for the main categories, which are costs and outcomes, and summarize them in overall measurement.	
Effect of uncertainty	25	Describe how uncertainty affects the results of the study. Report how the discount rate and time horizon were chosen, if applicable.	
Effect of the involvement of patients and others groups affected by the study	26	Report any differences in stakeholders involved in the study.	

Section/Topic	No	Guidance for reporting	Reported in section
Discussion			
Findings of the study, limitations, generalizations, and current knowledge	27	Describe how the main findings, limitations, and ethical or equity considerations were considered and how the results might affect stakeholders.	
Other relevant information			
Funding sources	28	Describe how the study was funded and any role of the donor in the identification, design, implementation, and reporting of the analysis.	
Conflict of interest	29	Report the authors' conflict of interest.	

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