CHI EVALUATION FRAMEWORK (CHIEF): GUIDANCE DOCUMENT

VERSION 1.0 JULY 2023

CENTRE FOR HEALTHCARE INNOVATION

Contents

Executive summary

The healthcare innovation landscape is constantly evolving, with new technologies and solutions being developed to improve patient outcomes and quality of life, increase efficiency, and reduce costs. Despite this, there is often a gap between the development of new technologies and their adoption and implementation in healthcare settings.

Healthcare organizations are often large and complex, with multiple stakeholders involved in decision-making. Each stakeholder may have different priorities and perspectives, which can make it difficult to reach a consensus on which technologies to adopt and how to implement them.

Some of the key factors in decision-making include:

- Perceived value of technology
- Impact on practice
- Barriers to adoption, such as technical challenges, regulatory or legal barriers
- Budget
- Delivery of the solution

The acceleration in innovation development calls to the identification and prioritization of value innovations that warrant further investment, adoption, and scalability, ensuring that resources are allocated to solutions that truly make a positive impact in healthcare.

To facilitate this, the Centre for Healthcare Innovation (CHI), together with stakeholders, developed the CHI Evaluation Framework, CHIEF. Combining rigorous evidence-based methodologies, stakeholder engagement on methods of evidence-generation, and a tiered evaluation approach, CHIEF helps to ensure that healthcare innovations are thoroughly assessed on its value proposition, enabling more informed decision-making on resource allocation for investment and implementation.

The processes involved to enable this include:

1. Working with solution developers and healthcare professionals in designing studies appropriate to the readiness level and evidence requirement of the solution to generate high-quality evidence,
2. Conducting appraisal of evidence by a team of trained independent clinicians to systematically evaluate the quality, relevance, and validity of evidence, and
3. Facilitating the evaluation process by applying the methodologies of the MCDA (Multi-Criteria Decision Analysis), offering benefits of a structured and transparent evaluation approach.

The framework aims to align with the quadruple aims of health, which encompass the core objectives of healthcare:

- Enhancing patient experience
- Improving population health
- Reducing healthcare costs, and
- Supporting healthcare providers

Foreword

Welcome to the CHI Evaluation Framework (CHIEF). CHIEF provides a comprehensive approach to guide decision-making by appraising and evaluating evidence-based solutions. It is designed to be flexible and adaptable, allowing it to be applied to a wide range of contexts including healthcare, public health, social services, and more.

CHIEF is the result of collaboration between experts in various fields, including epidemiology, biostatistics, health economics and decision science. It is built upon the principles of evidence-based medicine, which emphasizes the importance of integrating the best available evidence with clinical expertise and patient values to inform decision-making.

The development of this guidance document was guided by the CHI Evaluation Framework (CHIEF) Advisory Committee that comprises key representatives from:

Ministry of Health
ALPS Pte Ltd
A*Star Innovation & Enterprise Group
Centre for Healthcare Innovation
Centre for Innovation in Healthcare
Enterprise Singapore
Health Innovation Netherlands
Health Products Regulation Group
National Healthcare Group
National Health Innovation Centre
Research for Impact

Special acknowledgement to Centre for Healthcare Innovation – Clinical Research and Innovation Office (CRIO) and its specialist advisors for their contribution to the development of this document.

This document is designed to be used by solution developers, healthcare providers, and decision-makers, who seek to apply the processes and methods employed by CHIEF. It also serves to provide practical information and best practices on topics such as study design, usability and acceptability assessments, and health economics.

We hope that this framework will serve as a valuable tool for decision-makers, researchers, innovators, and practitioners to make informed decisions based on the best available evidence.

1. CHI Evaluation Framework (CHIEF)

1.1 Introduction

The CHI Evaluation Framework (CHIEF) is designed to be applicable across various healthcare contexts and settings. It provides a systematic and evidence-based approach to assess the value and impact of healthcare innovations. Offering clear guidelines and criteria for evaluation, it helps to enable informed decision-making and resource allocation.

The framework can be utilized in diverse healthcare settings, including hospitals, clinics, community health platforms, and digital health platforms. By adopting this framework, stakeholders across the healthcare ecosystem can benefit from a standardized and rigorous evaluation process, leading to improved patient outcomes and enhanced healthcare delivery.

1.2 Target audience

CHIEF is available to any organization seeking to evaluate innovation solutions at its pivotal developmental stages to determine resource allocation for investment and implementation.

The framework hopes to benefit stakeholders involved in the healthcare innovation ecosystem, including healthcare providers and decision-makers, researchers and innovators, industry, and patients and caregivers -

Healthcare providers & decision makers:
The tier-based evaluation framework provides a structured approach to effectively assess and prioritize healthcare innovations based on its potential for impact and value.

By using the framework, decision-makers can ensure that they are making informed decisions based on reliable evidence that have been appraised on scientific merit, and applicability to clinical decision making. [13]

Researchers and innovators:
Researchers and innovators can use the framework's methodologies and guidance to design rigorous studies and generate evidence on the effectiveness and value of healthcare innovations.

Industry:
By utilizing the framework, solution developers can align their development and investment efforts with the evolving needs and priorities of healthcare providers and decision-makers. This enables them to focus their resources on solutions that have a higher likelihood of adoption and scalability, increasing their chances of market success.

Patients and caregivers:
The framework provides a transparent and evidence-based approach to evaluating healthcare innovation solutions and promoting the adoption of high-quality and patient-centred innovations that can improve healthcare outcomes.

1.3 Scope of technologies

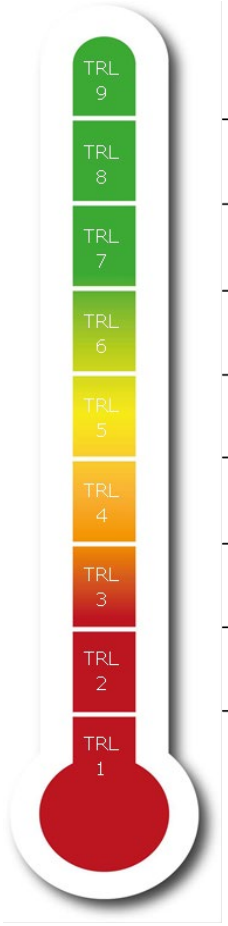
CHIEF is designed to provide a systematic approach to guide on study design and evaluate (1) medical technologies and (2) digital health technologies that are (3) technology readiness level 5 and above.

(1) Medical technologies:
Defined as "the technologies that diagnose, treat and/or improve a person's health and wellbeing, encompassing both low- and high-risk medical devices." [2]

(2) Digital Health Technology:
Based on WHO guidelines – Recommendations on Digital Interventions for Health Systems Strengthening, "the term digital health is rooted in eHealth, which is defined as the use of information and communications technology in support of health and health-related fields." [5]

(3) Technology Readiness Level (TRL)
This is a scale commonly used to evaluate and communicate the readiness level of new technologies or new applications of existing technologies.

Table 1
Technology Readiness Level (TRL)



TRL 9	Actual system proven in operational environment: The technology has been deployed and proven to be effective and efficient in a real-world operational environment
TRL 8	Actual system completed and qualified: The technology is fully developed, qualified, and ready for deployment in a real-world setting
TRL 7	System prototype demonstration in operational environment: A system prototype has been developed and demonstrated in an operational environment, showcasing its integration and usability
TRL 6	Technology demonstration in operational environment: The technology has been demonstrated in an operational environment, showing its effectiveness and readiness for integration
TRL 5	Technology validation in relevant environment: The technology has been tested in a relevant operational environment to demonstrate its functionality
TRL 4	Technology validation in lab environment: The technology has been tested in a controlled laboratory environment to validate its performance
TRL 3	Technology concept formulated: The technology concept is defined, and initial experiments or prototypes have been developed
TRL 2	Technology concept formulated: The technology concept is defined, and initial experiments or prototypes have been developed
TRL 1	Basic principles observed: The technology concept is based on scientific principles, but there is no practical application yet

Source: Reference 23

1.4 Engaging CHIEF

CHIEF is supported by a dedicated workgroup, comprising a project manager and scientific experts that work collaboratively to communicate and guide on the framework's processes and methods, and facilitate evidence appraisal and solution evaluation.

The project manager is responsible for the overall management and coordination of the framework and serves as the primary point of contact, addressing queries and assisting users throughout the framework's application.

The scientific experts provide consultation on research methodologies, study designs, cost-effectiveness considerations, and data analysis techniques.

Healthcare providers and solution developers coming together to explore feasibility of new solutions ready to be tested for TRL 5 and above can engage the workgroup to explore its services.

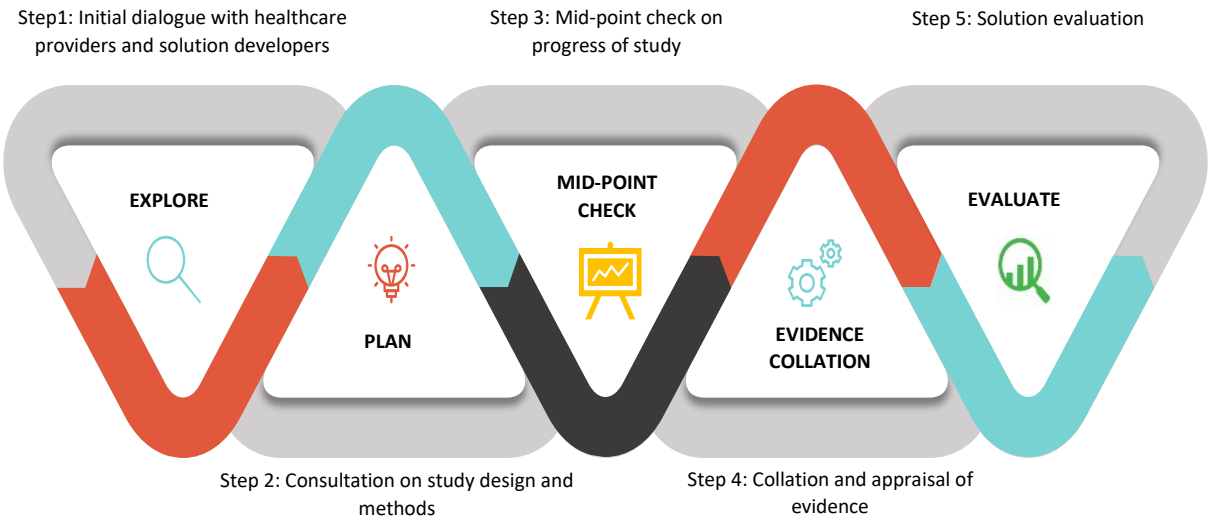
It is important to note that some of the services provided under the framework may incur charges. Interested parties may inquire about the charges and available services beforehand to ensure that they have a clear understanding of the costs involved in the process. The CHIEF workgroup will provide a clear breakdown of the services and associated cost, so that stakeholders can make an informed decision regarding the services they require.

We encourage stakeholders interested in engaging CHIEF to submit a contact form through this link - https://form.gov.sg/64b89c7495cfb90011f0a636

1.5 Work Process

This section provides an overview of CHIEF's work process to guide stakeholders through the evaluation journey -

Diagram 1
CHIEF work process



Step 1: Initial dialogue with healthcare providers and solution developers

The first step of the process is an exploratory session. The CHIEF workgroup initiates an initial dialogue with stakeholders who express interest in testing and evaluating new solutions. This dialogue serves as an opportunity to establish communication channels and understand the stakeholders' goals, requirements, and expectations. During this stage, the workgroup actively collaborates with stakeholders to pre-determine the specific value components upon which the solution will be assessed and evaluated.

Step 2: Consultation on study design and methods

Where a study needs to be conducted to gather evidence for evaluation, stakeholders involved in the design of the study are encouraged to engage with the CHIEF workgroup during the initial design phase to seek guidance and advice. It is important that the study design takes into account the specific data that needs to be captured to effectively assess review and assess the pre-determined value components established during the initial dialogue.

Step 3: Mid-point check on progress of study

To ensure the study progresses smoothly, the CHIEF workgroup will conduct a mid-point check on the study's progress. This check serves as an opportunity for stakeholders to provide updates on the study's progress, highlight any challenges encountered, and discuss the potential for adjustments in study design.

Step 4: Collation and appraisal of evidence

Once the study has been completed and trial data analysed, stakeholders are required to report results following relevant reporting guidelines such as the Consolidated Standards of Reporting Trials (CONSORT), Strengthening the Reporting of Observational Studies in Epidemiology (STROBE), etc., dependent on the study design. This is to ensure transparency, completeness, and standardized reporting, to facilitate the critical appraisal and synthesis of evidence.

Step 5: Solution Evaluation

Building on the collected evidence and appraisal, CHIEF proceeds with the evaluation of the solution by an independent and expert panel of clinicians and industry experts. The evaluation process encompasses a comprehensive assessment of the solution's attributes and performance against the pre-defined value components.

2 Exploratory session

2.1 Introduction

The exploratory session is an initial meeting between the CHIEF workgroup and stakeholders with vested interest in assessing and evaluating the solution. Solution developers are also encouraged to attend this session.

At this point, the CHIEF workgroup will seek to understand -

1. Solution type: Intended use and potential impact on the care pathway
2. Technology readiness level (TRL): Assessing the current stage of development and readiness of the solution, including any existing evidence or studies conducted
3. Evaluation objectives: Clarifying the specific goals and objectives of the evaluation, such as assessing the solution's effectiveness, safety, feasibility, or cost-effectiveness
4. Value components: Identifying the relevant value components that stakeholders would like to focus on, considering the intended use and impact of the solution
5. Study design: Discussing the study design and methodology, including the type of study and data collection methods
6. Data requirements: Determining the necessary data elements and variables that should be captured during the study to support the assessment of the solution's value components
7. Stakeholder expectation: Understanding the expectations of stakeholders regarding the evaluation outcomes and how results may inform decision-making processes
8. Timeline and resources: Discussing the estimated timeline and resources for the conduct of the study, and any potential challenges or constraints that may impact study design considerations and data collection

The information obtained at this stage plays a crucial role in guiding the subsequent actions and facilitating a tiered evaluation process.

2.2 Tiering and selection of value components

CHIEF employs a tiered evaluation approach that takes into account the readiness level and available evidence of the solution under evaluation. To achieve this, relevant value components are applied at each stage, taking into consideration the available evidence and the objectives of the evaluation.

At the earlier stages of readiness, the focus may be on assessing the feasibility and potential of the solution for further development, whereas later stages of development will focus on potential for clinical adoption and scale.

By tailoring the selection of evaluation criteria to the various stages of solution development, the evaluation process becomes more targeted and streamlined, focusing on the key aspects that are most relevant and meaningful for its advancement.

2.2.1 Stakeholder engagement in evaluation criteria selection

CHIEF recognises the importance of engaging stakeholders throughout the selection process of value components for evaluation.

Stakeholders such as healthcare providers, decision-makers, and funders (e.g., grant bodies) bring valuable insights and perspectives that shape the evaluation criteria. Their involvement ensures that the selected value components align with their priorities, expectations, and requirements. This will also help foster a sense of ownership and collaboration, ultimately enhancing the validity and applicability of evaluation outcomes.

2.2.2 Value components

To help determine the value components, we first highlight the pivotal stages at which evidence may be obtained to advise on –

- Potential for further development
- Potential for further investment/ early adoption
- Potential for adoption & integration
- Potential for scale

Table 2
Pivotal stages for evaluation

	Description	Clinical readiness/ qualifiers	Pivotal stages
TRL 1	Basic principles observed: The technology concept is based on scientific principles, but there is no practical application yet.	Conceptual stage: The clinical concept is defined, but there is no practical application or evidence of clinical feasibility yet.	
TRL 2	Technology concept formulated: The technology concept is defined, and initial experiments or prototypes have been developed.		
TRL 3	Technology concept formulated: The technology concept is defined, and initial experiments or prototypes have been developed.	Preclinical evidence: Preclinical studies or animal models have provided evidence supporting the clinical potential of the technology.	
TRL 4	Technology validation in lab environment: The technology has been tested in a controlled laboratory environment to validate its performance.	Technical validation: Further tests have shown consistent performance of the technology.	
TRL 5	Technology validation in relevant environment: The technology has been tested in a relevant operational environment to demonstrate its functionality.	Feasibility/ pilot studies: Verify the need with the intended users and assess how the proposed solution is received by relevant clinical environments	Potential for further development
TRL 6	Technology demonstration in operational environment: The technology has been demonstrated in an operational environment, showing its effectiveness and readiness for integration.	Expanded clinical validation: Further clinical trials or studies have shown consistent safety, efficacy/ effectiveness, and clinical utility of the technology.	Potential for investment/ early adoption
TRL 7	System prototype demonstration in operational environment: A system prototype has been developed and demonstrated in an operational environment, showcasing its integration and usability.	Clinical integration studies: The technology is shown to be safe and effective, and can potentially be successfully integrated into clinical workflows with demonstrated positive outcomes in real-world settings	Potential for adoption & integration
TRL 8	Actual system completed and qualified: The technology is fully developed, qualified, and ready for deployment in a real-world setting.	Clinical adoption and utilization: The technology is ready to be adopted by healthcare providers, with evidence of improved patient outcomes and efficiency in healthcare delivery.	
TRL 9	Actual system proven in operational environment: The technology has been deployed and proven to be effective and efficient in a real-world operational environment.	Long-term evidence and outcomes: Long-term clinical studies or real-world evidence have confirmed the sustained benefits and impact of the technology.	Potential for scale

Source: Adapted from 14, 21, 23

The proposed value components in the following tables for each pivotal stage serve as a foundation for discussion and can be tailored based on the specific solution type, context, and expected evidence. CHIEF values the diverse perspectives brought forth by stakeholders and recognises that different solution types may necessitate modifications to the proposed criteria.

The evaluation of each value component encompasses the use of evidence, which can be derived from current studies or cumulative evidence gathered from previous studies.

Table 3
Proposed value components for evaluation

Potential for further development *(Evidence from pre-clinical studies)*	**Potential for further investment/ early adoption** *(Evidence from initial clinical studies)*	**Potential for adoption & integration** *(Evidence from pragmatic/ real-world studies)*	**Potential for scale** *(Evidence from implementation studies)*
1. Quality of evidence • Completeness and consistency of reporting evidence[1] • Relevance and validity of evidence[2] 2. Clinical need[3] 3. Proposed solution • Differentiation[4] • Safety • Effectiveness[5]	1. Quality of evidence • Completeness and consistency of reporting evidence[1] • Relevance and validity of evidence[2] 2. Study design & results • Robust and unbiased estimates[6] 3. Need for intervention • Disease severity[7] (if applicable) • Size of population affected by disease[8] (if applicable) 4. Technology/ Intervention • Current interventions' limitations[9] • Improvement of efficacy/ effectivesness[10] • Improvement of safety & tolerability[11] • Improvement on reported outcomes, convenience & adherence[12] • Reliability[13] • Usability[14] • Public health interest[15] (if applicable) 5. Economics • Early cost effectiveness[16]	1. Quality of evidence • Completeness and consistency of reporting evidence[1] • Relevance and validity of evidence[2] 2. Study design & results • Robust and unbiased estimates[6] 3. Need for intervention • Disease severity[7] (if applicable) • Size of population affected by disease[8] (if applicable) 4. Technology/ Intervention • Current interventions' limitations[9] • Improvement of efficacy/ effectiveness[10] • Improvement of safety & tolerability[11] • Improvement on reported outcomes, convenience & adherence[12] • Reliability[13] (availability & non-failure) • Public health interest[15] (if applicable) 5. Early implementation outcomes • Usability[14] • Acceptability[17] • Appropriateness[18] • Feasibility[19] • Sustainability[20] 6. Economics • Cost-effectiveness[21] of intervention • Cost of use & maintenance[22] Others • Implementation risk management[23]	1. Quality of evidence • Completeness and consistency of reporting evidence[1] • Relevance and validity of evidence[2] 2. Technology/ Intervention • Evidence on sustained benefits and impact of technology 3. Implementation outcomes • Acceptability[18] • Adoption[24] • Appropriateness[19] • Feasibility[20] • Fidelity[25] • Coverage[26] • Sustainability[21] 4. Economics • Implementation cost[27] Others • Implementation risk management[23]

1. Extent to which reporting of evidence on the proposed intervention is complete (i.e., meeting international standards on reporting) and consistent with the sources cited

2. Extent to which evidence on the proposed intervention is relevant to the decision-making body (in terms of population, disease stage, comparator interventions, outcomes etc.) and valid with respect to international standards (i.e., study design etc.) and conclusions (agreement of results between studies)
3. Addresses a particular clinical need required by customers
4. Advantages that a product has over the state of the art and if it will more effectively meet customer needs than existing similar products
5. Qualitative parameter that measures the degree of success of a product concept in achieving the goals and determines whether it can provide the effect for which it was designed
6. Use of rigorous methodologies and statistical analyses that minimize biases, ensure validity, and provide reliable and credible findings
7. Severity of the health condition targeted by the proposed intervention with respect to mortality, disability, impact on quality of life, clinical course (i.e., acuteness, clinical stages)
8. Number of people affected by the condition (targeted by the proposed intervention) among a specified population at a specified time; can be expressed as annual number of new cases (annual incidence) and/or proportion of the population affected at a certain point of time (prevalence)
9. Shortcomings of current interventions in their ability to prevent, cure, or ameliorate the condition targeted by the proposed intervention; also includes shortcomings with respect to safety, convenience, or patient acceptance.
10. Capacity of the proposed intervention to produce a desired (beneficial) change in signs, symptoms, or course of the targeted condition above and beyond beneficial changes produced by alternative interventions. Includes efficacy and effectiveness data, as available.
11. Reduction in intervention-related health effects that are harmful or undesired compared to alternative interventions.
12. Capacity of the proposed intervention to produce beneficial changes in patient-reported outcomes (PROs) (e.g., quality of life) above and beyond beneficial changes produced by alternative interventions; also includes improvement in convenience to patients and adherence to treatment course.
13. Availability and non-failure; product does what users want when they want to use it.
14. Refer to usability
15. Nature of the health benefit provided by the proposed intervention at the population-level (e.g., impact on prevention, reduction in disease transmission, reduction in the prevalence of risk factors, etc.)
16. Refer to early health economics
17. Perception among stakeholders (e.g., consumers, providers, managers, policymakers) that an intervention is agreeable. Factors related – comfort, relative advantage credibility. (Additional refer to acceptability)
18. Perceived fit/ relevance of the intervention in a particular setting or for a particular target audience or issue. Factors related – relevance, compatibility, trialability, suitability, usefulness, practicability.
19. Extent to which an intervention can be carried out in a particular setting or organization. Related terms – practicality, actual fit, utility, suitability for everyday use.
20. Extent to which an intervention is maintained or institutionalized in a given setting. Related terms – maintenance, continuation, durability, institutionalization, routinization, integration, incorporation.
21. Refer to full health economics
22. Value spent to use solution, namely the product, energy, and maintenance
23. Refer to innovation risk management
24. Intention, initial decision, or action to try to employ a new intervention. Related terms – uptake, utilization, intention to try.
25. Degree to which an intervention was implemented as it was designed in an original protocol, plan, or policy. Related terms – adherence, delivery as intended, treatment integrity, quality of programme delivery, intensity, or dosage of delivery.
26. Degree to which the population that is eligible to benefit from an intervention actually receives it. Related terms – reach, access, service spread or effective coverage (focusing on those that need an intervention and its delivery at sufficient quality, thus combining coverage and fidelity), penetration (focusing on the degree which an intervention is integrated in a service setting).
27. Incremental cost of the delivery strategy (e.g., how the services are delivered in a particular setting). The total cost of implementation would also include the cost of the intervention itself

Source: Reference 3, 8, 9, 18

3 Study design and methods

3.1 Introduction

In the dynamic field of healthcare innovation, solutions can vary greatly in terms of their complexity, application, and intended outcomes. As a result, there is no one-size-fits-all approach or fixed methodology when it comes to designing studies for evaluating these solutions. Each study design must be tailored to the specific context and objectives of the innovation being evaluated.

When designing a study, it is essential to consider a range of factors that can significantly impact the research design and methodology. These factors encompass -

- Phase of the device's life cycle
- Type of device (therapeutic/ non-therapeutic/ support or companion etc)
- Working mechanism through which a device leads to risks, benefits, or less burdensome care
- Intended medical context or indication
- Intended users
- Prevailing care in the intended context
- Study objectives
- Resources available (Funding, personnel, infrastructure, time)
- Ethical considerations (Protection of study participant's rights, obtaining informed consent, addressing potential risks and benefits, and maintaining confidentiality) [12]

Further to that, it is important to adhere to certain guiding principles and best practices. Well-designed studies minimize biases, increase the reliability of study results, and ensure that the results are generalizable and applicable to the target population. Furthermore, robust study design allows for effective comparison with existing standards of care or alternative solutions, facilitating informed decision-making process.

CHIEF emphasizes the importance of this step and recommends in-depth exploration of the study design as it is crucial in ensuring that the evidence collected will be robust, valid, and reliable to support decision-making. The process of study design planning is an iterative one that should involve solution developers and inputs from experts in clinical fields, quantitative methodology, statistics, and health economics.

3.2 Study designs

The study design plays a crucial role in generating reliable evidence.

Early-stage innovations may require feasibility studies or pilot studies to determine whether they are worth further investment, while matured solutions may require more rigorous study designs to demonstrate safety, efficacy/ effectiveness, and comparative benefits.

Randomized controlled trials (RCTs) are widely considered the gold standard for evaluating medical technologies because they allow rigorous comparisons between treatment groups. However, randomised designs may not always be appropriate or feasible. Non-randomized comparative studies, observational studies, or systematic reviews are among the commonly employed designs, each offering distinct strengths and limitations. Separately, pragmatic studies conducted in real-world settings capture the contextual factors influencing technology performance and implementation.

To allow for evaluation on the adoptability or scalability of a healthcare solution, CHIEF recommends the following considerations when designing a study -

- Study population: Ensure that the study population is representative of the target population for the solution and that the study includes participants from diverse backgrounds and settings drawn from within the target population.

- Implementation outcomes: Incorporate implementation considerations that will allow for the evaluation of the solution's "implementability" and integration into clinical workflows during an effectiveness study. These include implementation outcomes such as acceptability, usability, and healthcare performance indicators of clinical workflow process, health outcomes and quality of life.

- Health economics: Include economic analysis where feasible to assess the cost-effectiveness and sustainability of the solution as well as to help decision-makers to make informed decisions about resource allocation and implementation of cost-effective new technologies.

3.2.1 Randomized controlled trials (RCTs)

RCTs are considered the gold standard for evaluating the efficacy and safety of new clinical solutions. RCTs involve randomly assigning participants to a treatment group (receiving the new clinical solution) or a control group (receiving a placebo or standard of care). This study design allows for comparisons between the treatment and control groups, minimizing bias and confounding variables.

RCTs can address a wide range of research questions, such as testing new drugs, surgical procedures, medical devices, behavioural interventions, and public health interventions.

There are three basic components of RCTs –

1. At least one test treatment and a comparator treatment
2. Randomization of treatment allocation
3. Outcome measure(s)

There are several common variants of RCTs that can be used, depending on the research question and available resources. The list of common variants is summarized under Table 4.

It is important for researchers to understand these common variants of RCT to design studies that are optimal for their research question and the resources they have available.

Table 4
Common Variants of Randomised Controlled Trials (RCTs)

Variants of RCT	Characteristics
Cluster	• Randomizes groups of individuals rather than individual participants. • Used when it is not feasible to randomize individuals or when the intervention is delivered at a group level. • Unit of study is a school or hospital etc. • Reduces risk of 'contamination', and practicality issues.
Cross-over	• Involves participants receiving multiple interventions in a randomized order.

	• Useful when comparing two or more interventions that cannot be administered simultaneously. • Only suitable if disease returns promptly with cessation of intervention (i.e. treatment has limited 'carry-over' effect).
N-of-one	• Also known as a single-subject or single-patient trial. • Focuses on studying the response of an individual patient to a particular intervention (Individual serves as his or her own control). • Typically involves alternating periods of treatment and placebo (or another treatment) in a randomized order. • Allows researchers to evaluate the effectiveness of the intervention specifically for that patient. • Often used in situations where there is uncertainty about the effectiveness of a treatment or when an individual's response to a particular intervention needs to be evaluated.
Non-inferiority	• Designed to compare a new treatment to an active comparator (i.e., 'head-to-head' study). • A pre-defined margin is set to determine the maximum difference considered clinically acceptable between the new treatment and the active control. • While 'new' intervention is less effective, 'traded-off' for other advantages of 'new' (e.g., cost, safety).
Parallel group	• To compare the effectiveness of two or more interventions or treatment groups (i.e., comparative effectiveness, "equivalence"). • Involves random allocation of participants to different groups, each receiving a different intervention or treatment (i.e., novel therapy/ standard treatment/ placebo/ alternative intervention).
Factorial designs	• Each participant is randomly assigned to a group that receives a particular combination of interventions or non-interventions. • The advantages of this approach over parallel comparison are its ability to efficiently investigate multiple interventions and detect interaction between different treatments. It also requires fewer patients and is less costly than conducting multiple parallel group trials.
Proof of concept	• Evaluates the feasibility and preliminary efficacy of a new intervention or treatment. • Smaller sample size compared to larger efficacy trials. • May also be used to assess the feasibility of various aspects, such as recruitment, adherence to intervention, data collection, and overall study procedures. • High internal validity – but tends to over-estimate efficacy. Lots of exclusions can be resulted in recruitment of "perfect" patients (i.e., very selective patients based on inclusion criteria). • Results less generalisable (external validity).
Pragmatic	• Evaluates real-world effectiveness and impact of an intervention in routine clinical practice. • May compare the intervention against existing standard of care or another active treatment commonly used in clinical practice.

	• Broad inclusion criteria to include diverse range of patients' representative of the target population in routine practice (Often GP based, open label and 'all comers' included). • Often have a parallel-group design with random allocation of participants to different interventions. • Excellent generalisability, but less internally valid.
Adaptive designs	• Evaluate effectiveness of an intervention or treatment using an adaptive design. • Allows for pre-planned modifications or adaptations to trial design based on interim analysis of accumulating data. • May incorporate various adaptive elements such as adaptive randomization, sample size reassessment, treatment arm selection, dose-finding. • Pre-specified criteria (decision rules) that guide the adaptations based on interim analysis results. • Advantage of flexibility which can enhance efficiency and reduce resource utilization.

Source: Reference 15

3.2.2 Non-randomized studies

Non-randomized studies, also known as observational studies, play a crucial role in medical technologies and digital technology research, especially when conducting randomized controlled trials (RCTs) is impractical or unethical. These studies are particularly valuable for evaluating interventions in real-world settings, assessing their effectiveness in routine clinical practice, studying long-term outcomes, or investigating rare diseases where participant recruitment for RCTs is challenging.

Despite their limitations and susceptibility to bias, non-randomized studies provide valuable evidence that informs decision-making and shapes healthcare practices. They offer insights into the safety, effectiveness, and real-world impact of medical technologies and digital interventions. Through careful analysis of data from these studies, researchers and healthcare professionals gain essential knowledge and understanding to make informed choices, ultimately leading to improvements in patient care.

Below is a summary of frequently used non-randomized study designs -

Table 5
Types of non-randomised studies

Study designs	Characteristics
Cross sectional	• Provides a snapshot of a population at one specific point in time. • Researchers collect data on both exposure and outcome simultaneously at one time point, enabling them to analyse associations between technology use and health outcomes in the studied population. • Important to note that while cross-sectional studies provide valuable insights, they do not establish causal relationships between technology use and health outcomes due to their observational nature and the lack of temporal sequencing in the data collection process.

Prospective Cohort	• A group of individuals with a specific condition or exposure are followed over time to observe outcomes. • In AI/medical technology research, these studies often include a cohort of digital health app users and a control group of non-app users with similar characteristics – – The control group acts as a comparison basis (or) serves as a reference standard against which the outcomes of the AI/MedTech are evaluated. – Any observed differences in health outcomes between the two groups can be attributed to the influence of the AI/MedTech, helping researchers understand its clinical impact.
Retrospective Cohort	• An observational research design used in epidemiology and medical research to identify a group of individuals with a common exposure or condition and track their outcomes over time. • Uses existing data, thus more efficient and economical compared to prospective studies. • Can include large sample size, allowing better statistical power and generalizability of the findings. • However, the quality and completeness of available data may vary, and there may be limitations in assessing variables of interest. • Not a strong standalone method, as they can never establish causality. This leads to low internal validity and external validity.
Case Control	• Observational study that compares individuals with a specific outcome (cases) to individuals without the outcome (controls) to assess the association between exposure and outcome. • E.g., a case-control study design for AI/MedTech for therapeutic solution allows the evaluation of the clinical effect of the AI/MedTech intervention by comparing individuals with the health condition of interest (cases) to a carefully matched control group without the condition. • May also be applied to estimate the impact of the AI/MedTech on the development or outcome of the health condition. • Particularly useful when conducting prospective randomized trials may not be feasible. • Valuable for assessing the diagnostic accuracy and performance of AI algorithms in clinical diagnosis. Such studies play a critical role in validating and evaluating AI-based diagnostic tools.
Single-arm: Before-and-after studies	• Participants act as self-controls or self-comparisons • Enables assessment of impact of a medical technology or digital intervention by comparing outcomes before and after its implementation. • Although they lack randomization, they can provide insights into the effectiveness of a technology within a specific setting. • An advantage over the two-group cohort design is that smaller sample sizes are often needed because of within-participant comparisons (whereas parallel designs produce between participant comparisons). However, as with paired (randomised) crossover trials, there is the problem that participants might improve for unknown reasons unrelated to the device (e.g., regression to the mean or placebo effect), which requires a sufficient washout period.

	• Without a control group, it is challenging to attribute observed changes solely to the intervention, as other factors or confounding variables could contribute to the outcomes. • This design is also only possible if the target disease is chronic and not progressive. For acute disease states (i.e., rapidly changing (unstable) conditions) that are either self-limiting or progressive, such designs are not feasible because the true effects of the product are difficult to isolate from the natural history. • Findings may have limited generalizability due to the specific characteristics of the study population and setting, making it challenging to extrapolate the results to other populations or context. • In certain cases, pre-post-test single-arm studies can serve as an initial step to provide evidence for further investigations using more robust study designs, such as randomized controlled trials.

3.2.3 Pragmatic Studies

Pragmatic studies are designed to evaluate the effectiveness of an intervention in real-world clinical practice settings using a heterogeneous population. [6]

Unlike traditional randomized controlled trials (RCTs) that focus on efficacy under ideal conditions, pragmatic studies aim to capture the variability that occurs in routine clinical care and provide real-world insights from everyday practice.

Several important factors are taken into account in the design of a pragmatic study [6, 7], including:

- **Inclusion criteria:** Broad inclusion criteria to include a diverse patient population reflecting real-world clinical practice. This allows for a more representative sample of patients with varying patients characteristics, comorbidities, and treatment preferences.

- **Study Setting:** Pragmatic studies are often conducted in real clinical settings, such as primary care clinics or community hospitals, and utilizing existing infrastructure and involving routine healthcare providers (i.e., routine care services), and the trial can better capture the complexities of real-world treatment decisions.

- **Randomization and allocation:** Randomization techniques may be used in pragmatic studies, but pragmatic randomization strategies that minimize disruption to routine care are often used. These may include cluster randomization, in which groups of patients or clinics are assigned to different treatments, or the use of electronic health records to facilitate randomization and treatment allocation.

- **Outcome Measures:** Pragmatic studies focus on patient-centred outcomes relevant to real-world decision-making. Pragmatic studies can evaluate multiple outcomes that are important to patients and can be more patient-centred than traditional clinical trials, and measuring outcomes that matter to patients and providers, the study results are more applicable to real clinical practice. In addition, pragmatic studies now often include health economic evaluations to examine cost-effectiveness. [22]

- **Comparative Effectiveness: Pragmatic** studies are designed to directly compare different treatments or interventions that are commonly used in routine clinical practice. The goal is to generate evidence that

helps clinicians and patients make informed choices among available options, taking into account trade-offs among clinical effectiveness, safety, cost, and other factors.

Overall, the design of a pragmatic study aims to bridge the gap between research and practice by providing evidence that is applicable to real-world clinical decision-making.

By considering patient variations and focusing on meaningful and impactful outcomes, these studies offer valuable insights into the effectiveness and comparative effectiveness of treatments in routine care settings.

3.3 Evidence level

Level of evidence plays a crucial role in assessing the quality and strength of evidence generated from studies. It provides a systematic framework for evaluating the reliability and validity of findings, helping to guide evidence-based decision-making in healthcare.

The Centre for Evidence-Based Medicine (CEBM) has developed widely recognised and used classification system for levels of evidence. This system assigns different levels to various study designs, reflecting the hierarchy of evidence based on the rigor and quality of research methodologies.

Table 6 serves as a general recommendation and starting point for considering appropriate study designs. However, it is important to note that these recommendations are not meant to be rigid or definitive rules. The selection of study design should be tailored to the specific context, research question, and feasibility of conducting certain types of studies. It is essential to consider the unique characteristics and requirements of each healthcare innovation to determine the most appropriate study design for generating valid and reliable evidence.

Table 6
Study Designs and level of evidence for primary research questions

Level of Evidence (Highest to lowest)	Study designs			
	Therapeutic Studies – Investigating the Results of Treatment	Prognostic Studies – Investigating the Effect of a Patient Characteristic on the Outcome of Disease	Diagnostic Studies – Investigating a Diagnostic Test	Economic and Decision Analysis – Developing an Economic or Decision Model
Level I	High quality randomized controlled trial with statistically significant difference but narrow confidence intervals Systematic review[2] of Level I randomized controlled trials (and study results were homogeneous)	High-quality prospective study[4] (all patients were enrolled at the same point in their disease with ⩾ 80% follow-up of enrolled patients) Systematic review[2] of Level I studies	Testing of previously developed diagnostic criteria in series of consecutive patients (with universally applied reference "gold" standard) Systematic review[2] of Level I studies	Sensible costs and alternative; values obtained from many studies; multiway sensitivity analysis Systematic review[2] of Level I studies

Level II	Lesser-quality randomized controlled trial (e.g., <80% follow-up, no blinding, or improper randomization) Prospective[4] comparative study[5] Systematic review of Level II studies or Level I studies with inconsistent results	Retrospective[6] study Untreated controls from a randomised controlled trial Lesser-quality prospective study (e.g., patients enrolled at different points in their disease or <80% follow-up) Systematic review[2] of Level II studies	Development of diagnostic criteria on basis of consecutive patients (with universally applied reference "gold" standard) Systematic review[2] of Level II studies	Sensible costs and alternatives; values obtained from limited studies; multiway sensitivity analysis Systematic review[2] of Level II studies
Level III	Case-control study[7] Retrospective[6] comparative study[5] Systematic review of Level III studies	Case-control study[7]	Study of non-consecutive patients (without consistently applied reference "gold" standard) Systematic review of Level III studies	Analysis based on limited alternatives and costs; poor estimates Systematic review[2] of Level III studies
Level IV	Case series[8]	Case series	Case-control study Poor reference standard	No sensitivity analysis
Level V	Expert opinion	Expert opinion	Expert opinion	Expert opinion

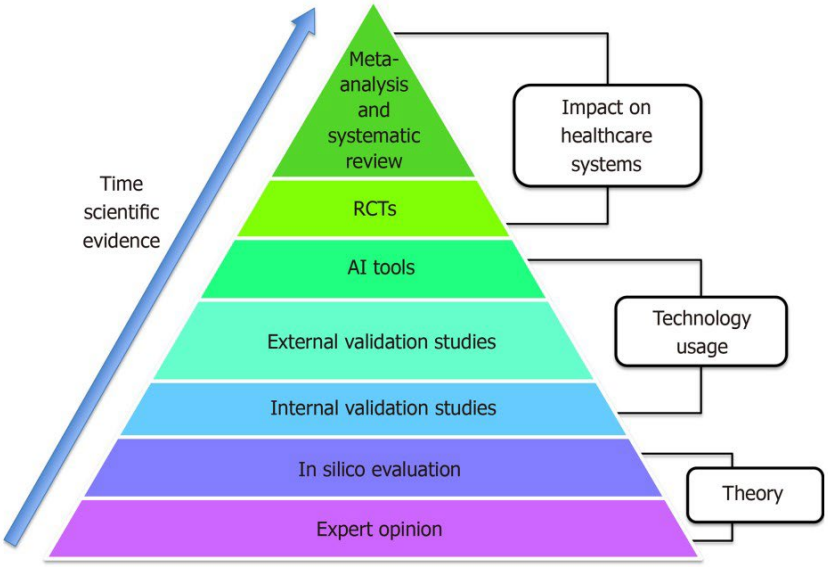
1. A complete assessment of the quality of individual studies requires critical appraisal of all aspects of study design
2. A combination of results from two or more prior studies
3. Studies provided consistent results
4. Study was started before the first patient enrolled
5. Patients treated one way (e.g., with cemented hip arthroplasty) compared with patients treated another way (e.g., with cementless hip arthroplasty) at the same institution
6. Study was started after first patient enrolled
7. Patients identified for the study on the basis of their outcome (e.g., failed total hip arthroplasty), called "cases" are compared with those who did not have the outcome (e.g., had a successful total hip arthroplasty), called "controls"
8. Patients treated one way with no comparison group of patients treated another way.

Source: Reference 16

Artificial Intelligence (AI) technologies has gained significant traction in the healthcare context, revolutionizing various aspects in healthcare delivery and decision-making.

When testing AI innovations in healthcare, robust study designs are of utmost importance. Figure 1 illustrates the different study designs used to test AI-based interventions, with the tip of the pyramid representing the strongest methodological analysis to reach conclusions on impact.

Figure 1
The artificial intelligence evidence-based medicine pyramid



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Note: A pyramid for artificial intelligence scientific evidence is proposed. Starting from the bottom and moving to the top, emerging results are becoming increasingly solid and strong. The two lowest rungs are the theory followed by the third, fourth and fifth steps that represent studies analysing the use of artificial intelligence (AI) in clinical practice. From creation of the model with internal validation, we move towards external validation studies and the creation of usable real instruments (AI tools). The penultimate step [randomized controlled trials (RCTs)] and the tip of the pyramid (meta-analysis and systematic reviews) represent the strongest methodological analysis to reach conclusions on the real impact of this technology on healthcare systems. If we then imagine the support base of the pyramid, we have the necessary tools for each step of clinical research in AI applied to the intensive care unit: Electronic health record, solid big data systems, internet of things technologies and models of explainable AI.

Source: Reference 4

3.4 Additional considerations in study design

Care Pathway

The care pathway is crucial for evaluating effectiveness and costs of health technologies, with an emphasis on understanding how a specific technology fits into the overall patient care process and its impact on outcomes and costs. It covers the complete series of tests, treatments, and interventions a patient experiences from the initial assessment to the final clinical outcome(s).

The comparative study designs in the context of care pathways requires modified care pathway (with new-technology) and standard usual care pathway (without the new-technology). This comparative care pathway design (either randomized or non-randomized) may provide direct evidence of the benefits or added benefits of a new technologies use for health or health care.

It also provides an opportunity to evaluate the clinical effectiveness, safety, cost-effectiveness, and economic considerations such as cost savings or increased efficiency of the entire care pathway. This may impact overall expenses and resource utilization and resource allocation, able to identify opportunities for reducing costs while improving the overall efficiency of care delivery.

Dealing with Confounding and Bias

Dealing with confounding and bias is crucial in study design and analysis to ensure accurate and reliable results.

Bias refers to systematic errors in the design, conduct, or analysis of a study that can affect the validity of the results.

Confounding is a type of bias that refers to the presence of factors that are associated with both the exposure and outcome of interest, potentially leading to distorted or misleading results. This can be prevented by identifying major confounding variables and adjusting those during the study design stage e.g., through matching, stratification, and random allocation. Any remaining confounding effects can be adjusted during the data analysis stage e.g., through stratified analysis, propensity score match and adjusted model.

It is important to engage a multidisciplinary team that includes researchers, statisticians, and subject matter experts who can provide insights and expertise in identifying potential confounders, selecting appropriate study designs, implementing rigorous data collection and analysis methods, and considering strategies to minimize bias.

3.5 Study protocol

CHIEF recognises the importance of robust and well-designed study protocols in ensuring the validity and reliability of research outcomes.

To support stakeholders in this endeavour, CHIEF provides a study protocol template that has been established using standard guidelines such as (SPIRIT) Standard Protocol Items: Recommendations for Interventional Trials, that closely mirrors the CONSORT (Consolidated Standards of Reporting Trials) statement.

The study protocol encompasses detailed guidance for each of its section, providing support to stakeholders in designing their research investigations. These guidelines help ensure that the study protocol includes all essential components and follows established best practices.

As part of the evaluation, study protocols must be submitted to the CHIEF workgroup to be assessed on the appropriateness and robustness of the study design, including the research question, participant selection criteria, intervention details, outcome measures, data collection methods, and statistical analysis plan. This process promotes transparency, accountability, and the generation of reliable evidence to inform decision-making.

4 User experience

4.1 Introduction

Healthcare innovations encompass a wide range of products, services, and technologies that aim to improve patient outcomes and the overall healthcare system. It is thus imperative that these innovations are first well-received by all potential user populations.

CHIEF recommends the assessment of these innovations in terms of user experience, so as to determine the potential uptake of the proposed solution, and feasibility of any workflow or process redesign associated with it.

Neglecting the involvement of users can result in a product that is not fit for purpose, leading to poor adoption rates, and ultimately hindering the potential benefits of the technology. It is therefore imperative to actively engage them throughout the product development and implementation process to enhance the likelihood of successful adoption and sustained benefits.

Users referred to here are persons who interact with a product or service being evaluated. In healthcare, users may include patients, caregivers, healthcare providers, and other stakeholders involved in the delivery of care.

4.2 Usability and acceptability assessments

Usability
Described by the International Organization for Standardization (ISO), usability is "The extent to which a product can be used by specified users to achieve specified goals with effectiveness, efficiency, and satisfaction in a specified use context", and where -

- Effectiveness: The accuracy and completeness with which specified users can achieve specified goals in particular environments.
- Efficiency: The resources expended in relation to the accuracy and completeness of goals achieved.
- Satisfaction: The comfort and acceptability of the work system to its users and other people affected by its use.

To assess usability, five key quality components should be considered -

Table 7
Usability – Key quality components

Effectiveness	Assessing the effectiveness of a solution involves evaluating how well it achieves its intended purpose and goals. In usability surveys, users should be asked about the solution's ability to address their specific needs and whether it facilitates efficient completion of tasks or processes.
Efficiency	This focuses on the speed and ease with which users can accomplish tasks using the solution. Surveys should inquire about the speed and accuracy with which users can accomplish their goals, and the clarity of instructions provided.

Learnability	Pertains to how easily users can grasp and use the solution, especially for new users. Surveys should explore users' initial experience with the solution, their perceived ease of learning to use it, and the availability of adequate training and support.
Satisfaction	This reflects the overall user contentment with the solution. Surveys can gauge satisfaction levels by asking on overall experience, the likeliness to recommend the solution to others, and their overall level of comfort while using it.
Error prevention and recovery	Understanding how the solution handles errors and user mistakes is essential for assessing usability. Surveys should inquire about the clarity of error messages, the ease of recovery from errors, and any potential risks or safety concerns related to the solution.

Source: Reference 25

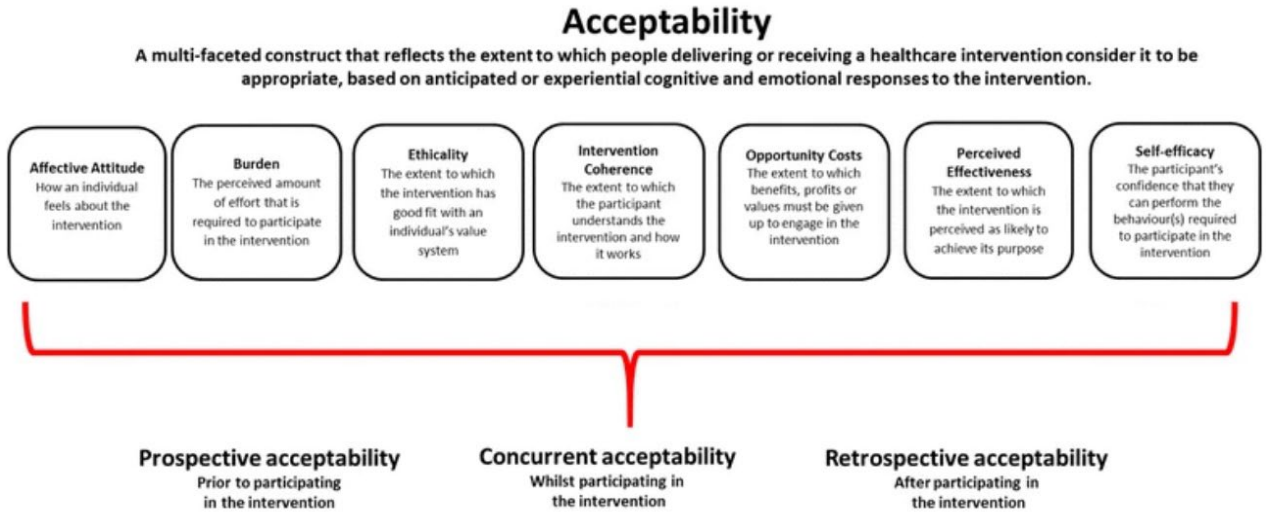
Acceptability

Acceptability is a multi-faceted construct that reflects the extent to which people delivering or receiving a healthcare intervention consider it to be appropriate and agreeable, based on anticipated or experienced cognitive and emotional responses to the intervention. [19]

The theoretical framework of acceptability comprises seven component constructs -

Figure 2

Theoretical framework of acceptability



Source: Reference 19

It is proposed that acceptability can be assessed from two temporal perspectives – prospective/ forward-looking, and retrospective/ backward-looking, and at three different time-points in relation to the intervention delivery period. [20]

Combining multiple assessments can provide a comprehensive understanding of the user experience. In designing the assessments, consider using established frameworks or validated instruments to ensure reliability and validity.

4.3 Designing usability and acceptability assessments

When designing usability and acceptability assessments, CHIEF recommends following a systematic methodology to ensure reliable and informative results -

1. Methodology
   Aim for mixed-methods approach that combines qualitative and quantitative data collection methods. This can help gather comprehensive insights into users' experiences and perceptions of the solution.

2. Define the assessment objectives
   Clearly articulate the goals and objectives of the assessment. Determine what specific aspects of usability and acceptability you want to evaluate and what insights you aim to gather from the assessments.

3. Define the target user populations
   Determine the specific user populations or user groups that will be involved in the assessment process. Consider the different stakeholders who will interact with the solution, such as patients, care givers, healthcare providers, administrators, or other relevant individuals. Identify the characteristics, demographics, and relevant background information of each user population.

4. Context of use
   Evaluate the context in which the solution will be used, such as clinical settings, home environments, or specific healthcare workflows. Understand the tasks and activities that different users will perform with the solution and how it fits into their existing routines.

5. Data collection tools
   Develop or adapt data collection tools, such as surveys, interviews, or observation protocols, to gather information on usability and acceptability -

   - Formulate questions that are clear, straightforward, and easy to understand. Avoid ambiguous language and use simple terminology.
   - When designing surveys, utilize Likert scale or rating-based questions to measure user perceptions on a quantitative scale, allowing for easy data analysis and comparison.
   - Include open-ended questions to allow users to provide qualitative feedback, highlighting specific aspects they find beneficial or challenging.

6. Sample Selection
   Develop a sampling strategy to ensure representative participation from each user population. Use random or purposeful sampling methods to select participants who can provide meaningful insights and experiences.

7. Pilot testing
   Where applicable, pilot testing the assessment tools with a small group of users or testers can help identify any potential issues of areas for improvement in the tools. This can allow for refinements before conducting the assessments on a larger scale if needed.

8. Establish assessment procedures
   Clearly define the procedures for conducting the assessments, including participant recruitment, data collection methods, and data analysis techniques. Provide detailed instructions to assessors on how to administer the assessments and ensure consistency in data collection.

5 Health economics

5.1 Introduction

Health economic plays a vital role in evaluating the potential value of innovations and supporting decision-making throughout the various stages of development.

The general scope of health economic analysis is to evaluate the costs and clinical effectiveness of new interventions in comparison to standards of care. The primary goal is to assess value for money, cost-effectiveness, and economic implications of new solutions compared to existing standard treatments, technologies, or practices. In addition, Health economics studies can help identify and address barriers to successful adoption of new healthcare interventions.

Given the tiered evaluation system employed by CHIEF, it is important to consider the application of health economics in a tiered manner, aligned with the readiness level of the innovation.

5.2 General considerations in health economics studies

When conducting a health economics study, it is important to consider various factors to ensure a comprehensive and robust analysis.

Factors include -

- Measure of the estimated treatment effect
- Choice of comparators
- The care pathway
- Clinical outcomes
- Estimates of clinical effectiveness
- Assessment of data quality, validity, robustness, and generalizability
- Currency, price date, and conversion
- Perspectives
- Time horizon
- Discounting
- Choice of model and model assumption
- Characterizing uncertainty
- Characterizing heterogeneity
- Cost categories
- Evidence on resource use and costs

Readers are encouraged to refer to the Appendix 1 of the guidance document for further details on the factors highlighted.

5.3 Types of health economics analyses

There are different types of health economic analyses, which vary in their methods and perspectives.

The appropriateness of a particular method of health economic analysis will also depend on various circumstances, the rationale for the study objectives, and the perspective. In addition, there are factors that

may influence the choice of health economic analysis, such as data availability, stakeholder involvement, ethical issues, and uncertainty.

Therefore, it is essential to consult relevant experts and follow the standard reporting guidelines before conducting or interpreting a health economic analysis.

The following are the common types of economic evaluations used in healthcare decision-making in the context of priority settings -

- Cost-Effectiveness Analyses (CEA)
- Cost-Utility Analyses (CUA), and
- Cost-Benefit Analyses (CBA)

These evaluations help decision-makers prioritize healthcare interventions by considering the costs and benefits associated with each option/intervention, and for determining the most efficient use of resources to help maximize the value of healthcare resources.

Table 8
Cost-Effectiveness Analyses (CEA) – Description and Considerations for Use

Type	**Description**
Cost-Effectiveness Analyses (CEA)	• Compares the costs and health outcomes or benefits of two or more different interventions, programs, or treatments. • It aims to determine which option provides the best value for money by considering both the costs incurred and the effectiveness achieved. • Measurement of health outcomes/clinical effectiveness involves estimating changes in health status, disease progression, or other relevant outcomes; outcomes are measured in a single natural unit (e.g., life-years gained, disease case averted etc.).
	Considerations for their usefulness
	<u>Resource allocation</u> • Helps determine the most efficient use of resources by assessing the relationship between costs and health outcomes. • By comparing costs and outcomes across different interventions, it enables decision-makers to prioritize interventions, programs, or healthcare services that can offer the greatest value (or) most health benefit. • Supports evidence-based decision-making and resource allocation, ensuring efficient use of limited resources and maximizing the desired outputs within the available resources. <u>Efficiency and value</u> • Considering technical efficiency when conducting CEA, policymakers and healthcare decision-makers can identify interventions or healthcare delivery strategies that provides the maximal health care for a given cost or delivering a certain service at a minimal cost.

Source: Reference 10, 24

Table 9
Cost-Utility Analyses (CUA) – Description and Considerations for Use

	Description
Cost-Utility Analyses (CUA)	• Cost-utility analysis (CUA; a specific type of cost-effectiveness analysis) used to compare their relative costs and outcomes of different interventions, programs, or treatments, with a focus on health-related quality of life. • The outcomes of interventions are measured in terms of time adjusted health utility and expressed as quality-adjusted life years (QALYs), which combine the quantity and quality of life experienced by individuals as a result of an intervention. • Health utility usually determines the value for a particular health state using the EQ -5D or SF -6D measurement tools to measure quality of life, which also allows for comparisons across conditions and interventions.
	Considerations for their usefulness
	<u>Resource allocation</u> • Aids decision-makers in allocating healthcare resources optimally by considering the trade-offs between different interventions and consider the optimal allocation of healthcare resources to maximize health benefits in terms of QALYs gained within a specific budget constraint. • Helps determine the most cost-effective mix of interventions that collectively provide the greatest health QALYs units gain for the available expenditure. <u>Efficiency and value</u> • Provides a quantitative measure of efficiency and value in healthcare resource allocation and efficient utilization of healthcare resources. • Allows decision-makers to compare the cost-effectiveness of different interventions and make informed choices about resource allocation to maximize health benefit. • By identifying interventions that generate higher health gains for a given level of expenditure, CUA contributes to the efficient utilization of healthcare resources.

Source: Reference 10, 24

Table 10
Cost-Benefit Analyses (CUA) – Description and Considerations for Use

	Description
Cost-Benefit Analyses (CBA)	• A form of comparative economic analysis that evaluates two or more programs or policy alternatives in terms of their relative costs and outcomes. • Both the costs and outcomes are expressed in monetary terms. • In principle, it should value the interventions relevant costs and outcomes based on the preferences of those affected (i.e., the individuals' willingness to pay).
	Considerations for their usefulness

	Resource allocation • Compares costs and health consequences of two or more programs with the health consequences measures in monetary units. • Allows for the conversion of both monetary and non-monetary benefits into a common unit (usually monetary terms) for comparison on the net economic benefit across different options (including to those outside of the healthcare sector, e.g., productivity gain). • Helps determine optimal allocation of resources by selecting the option that provides the highest net economic benefit. • Useful when making decisions that require a comprehensive assessment of all costs and benefits, including monetary (e.g., costs) and non-monetary factors (e.g., time savings, productivity gains and environmental benefits). Efficiency and value • Helps decision-makers allocate resources efficiently by comparing the costs and benefits of different options. • Provides a systematic framework to evaluate alternative uses of resources and identify the option that maximizes net benefits while minimizing resource utilization. • Considers opportunity costs, which refer to the value of the next-best alternative that is forgone or sacrificed when choosing one option or course of action over others. (Opportunity Costs helps assess the trade-offs involved in making choices and involves comparing the benefits and drawbacks of different options) • By weighing the benefits of a project against its costs, decision-makers can ensure that resources are allocated to the most valuable endeavours and avoid wasteful or less beneficial activities. • Enables the evaluation of both monetary and non-monetary benefits. Encourages the consideration of intangible benefits such as improved quality of life, environmental preservation, or social well-being. • By assigning a monetary value to these non-monetary factors, CBA provides a comprehensive assessment of value. • Can therefore consider allocative efficiency across different sectors/across society.

Source: Reference 10, 24

5.4 Early health economics

The benefits of using economic evaluation iteratively during the technology development process have been acknowledged in literature.

At the early stages of development, when limited information is available, health economics can provide preliminary insights into the potential value of innovation. This may include assessing the feasibility, potential cost-effectiveness, and potential economic impact of the innovation based on existing evidence or assumptions. It aims to provide initial insights into whether the innovation has the potential to deliver value in terms of its costs relative to its expected outcomes. However, this preliminary assessment may involve simplifications and assumptions due to the lack of robust data, and the results should be interpreted with caution.

For this purpose, CHIEF recommends the opportunistic collection of data for health economics evaluation at the earliest possible stage, for example, during initial clinical studies.

CHIEF recommends the following economics studies that can be incorporated during initial clinical studies -

1. Cost-effectiveness analysis (CEA)
2. Health-related quality of life assessments: Studies at pivotal trials often collect data on health-related quality of life measures using validated instruments. This information can be used to conduct utility-based analysis, such as cost utility analysis (CUA), to evaluate the impact of the intervention on patients' quality-adjusted life years (QALYs) and assess its cost-effectiveness
3. Resource use and cost analysis: Resource utilization data can also be collected to estimate the costs associated with the intervention, including direct medical costs, indirect costs, and healthcare utilization patterns (where possible).

In addition, systematic review, and collection of other available evidence from the initial clinical study and any external sources can serve to strengthen the cost-effectiveness evidence.

It is important to note that conducting early health economics studies early planning and coordination to collect the necessary data and incorporate economic endpoints into the study design. A larger sample size would be required to obtain statistically significant results.

5.5 Full health economics

As the innovation progresses to later stages of development, more robust health economics can be conducted. This may involve comprehensive cost-effectiveness analysis, budget impact assessments, or economic modelling studies. These evaluations can provide valuable insights into the economic implications of adopting the innovation within the healthcare system, considering factors such as costs, outcomes, resource utilization, and long-term sustainability.

For this purpose, CHIEF recommends the conduct of full health economic studies alongside pragmatic/ implementation studies. Health economics studies that can be conducted at this stage include -

1. Cost effectiveness analysis (CEA) in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines

2. Cost utility analysis for time adjusted utility which reflects a measure of value for the health state (e.g., QALYs)

3. Budget impact analysis (BIA)

The budget impact analysis (BIA) is an economic assessment that can be considered to evaluate the affordability and sustainability of a proposed intervention or new program by estimating its impact on the overall budget of the healthcare system or organization.

It helps decision-makers understand the potential costs associated with the intervention and make informed choices regarding adopting the intervention, making changes to existing practices, and resource allocation.

CEA and BIA can complement each other in the decision-making process. While CEA provides insights into the cost-effectiveness of interventions, BIA offers a comprehensive understanding of the financial implications and affordability.

BIAs have six primary elements [1]:

1. Treated population size

Determine population currently treated for the disease indication of interest.

2. Time horizon
   This is typically chosen on the basis of the requirement of the healthcare decision-maker, rather than on the duration of the impact of the new treatment (as for a cost-effectiveness analysis).

3. Treatment mix
   The determination of the mix of interventions currently used for the indication and the predicted change in that mix if the new intervention is made available.

4. Intervention costs
   Costs associated with the current and new interventions should include some or all of the following, depending on the type of intervention: acquisition or labour, other equipment, monitoring, and adverse event of complication costs.

5. Other healthcare costs
   Estimate of the impact of the new intervention on other indication-related costs, excluding intervention costs.

6. Presentation of results

In addition to the above, BIAs generally include sensitivity analyses to assess the impact of the input parameter uncertainty. [1]

6 Risk management

6.1 Introduction

Effective risk management is critical throughout the various stages of innovation development of new healthcare solutions, to ensure that potential risks are identified, evaluated, and managed effectively.

Healthcare organizations are faced with numerous risks that are highly interdependent, including those related to patient safety, cybersecurity, compliance, and reputation. When testing and implementing new healthcare solutions, there is a need to conduct a comprehensive risk assessment to identify and evaluate potential risks, prioritize risk mitigation measures, and ensure that risks are managed effectively.

International standards such as ISO 31000 provide guidance on risk management principles and a framework for risk management processes that can be applied. Further, healthcare organizations have their own enterprise risk management (ERM) policies in place to ensure that they are adequately managing risks across all domains.

Risk domains, or categories/ areas of risks is a method that most organizations use to segregate risks into manageable groupings. The risk domains defined in healthcare organizations may vary, depending on the organization's size, scope of services, and other factors.

Examples of risk domains relevant to healthcare organisations include -

- Safety of patient, staff, or public (physical/ psychological harm)
- Patient experience
- Quality and professional standards/ guidelines
- Objectives/ projects deliverables, budget, and time
- Business continuity
- Adverse publicity/ reputation
- Information governance/ information technology
- Finance and assets
- Complaints/ claims
- Staffing and competence, etc [17]

In addition to defining the risk domains, healthcare organizations' policies typically include guidance on the use of risk matrices to evaluate and prioritize risks. The risk matrix used by an organization may be customized to reflect the specific risks and priorities of the organization. [11]

Stakeholders, including healthcare providers, vendors, should refer to the ERM policies of the healthcare organizations they work with to ensure that they are complying with the organization's risk management framework. Compliance with the organization's risk management policies helps to ensure that stakeholders are aware of the potential risks associated with the implementation of new innovations and that appropriate risk management strategies are in place to mitigate those risks.

6.2 Stakeholders involved in the risk management process

Healthcare professionals involved in the testing and implementation of new solutions can involve stakeholders such as department managers, data managers, systems and technology managers in the risk management process.

Different stakeholders have different perspectives and experiences that can help identify risks and prioritize them according to their potential impact on patient safety, quality of care, integrity of systems, and other key factors.

The stakeholders involved can then help to develop risk management strategies that are appropriate for the specific risks identified and the context in which they occur. This ensures that the strategies are effective and feasible to implement.

6.3 Identifying potential risks

Before testing or implementing a new solution, healthcare professionals must first identify potential risks that could arise during the test phases or implementation process. This can include risks related to patient safety, data security, cybersecurity, workflow disruption and more.

6.4 Analyse and evaluate risks

Once potential risks have been identified, healthcare professionals should analyse and evaluate each risk to determine its likelihood of occurrence and potential impact or severity of harm. In healthcare organizations, decision-support tools such as risk matrices that allow standardized process of grading risks are commonly used. This is a systemic approach that can help determine and rank the risk level to allow prioritization of risks and define those that need to be controlled first.

6.5 Implement risk mitigation strategies

Risk mitigation strategies should then be developed, and carefully reviewed to determine those that are feasible to be implemented to prevent or control the risks identified. These strategies, once implemented, should be monitored on their effectiveness. This can include tracking the number of incidents related to each risk and assessing the effectiveness of each mitigation strategy in reducing those incidents.

6.6 Post implementation monitoring

Post monitoring of new solutions should be conducted so that organizations can proactively assess the performance, safety, and effectiveness of the implemented solution, ensuring the well-being of users and optimizing benefits. This also allows for detection and management of any unforeseen risks that may arise in real-world settings.

7 Evidence collation and appraisal

This stage involves the submission of post-study reports and, where applicable, meta-analysis from solution developers and the clinical study project team for appraisal and evaluation.

The evidence collation process is a crucial step, as it ensures all relevant evidence is collected and reviewed for the assessment of solutions.

Study reports submitted should adhere to reporting standards such as CONSORT (Consolidated Standards of Reporting Trials) statement on randomized controlled trials, STROBE guidelines for observational studies, PRISMA for systematic reviews and meta-analysis, and COREQ for qualitative research, so as to ensure that the reporting is comprehensive, transparent, and methodologically sound.

Evidence related to health economic studies should be reported following the CHEERS (Consolidated Health Economic Evaluation Reporting Standards) guidelines. It is important to include results of any sensitivity analysis conducted to assess the robustness of the results to changes in parameters and assumptions. Sensitivity analysis helps evaluate the uncertainty associated with the analysis.

EQUATOR (Enhancing the QUAlity and Transparency of health Research) network is a valuable resource that provides a comprehensive collection of reporting guidelines for different study designs and research methodologies. The reporting guidelines offer detailed recommendations and checklists to ensure transparent and comprehensive reporting. Refer to https://www.equator-network.org for the full list reporting guidelines.

Evidence submitted will be appraised based on -

Quality of evidence

- Completeness and consistency of reporting evidence - Extent to which reporting of evidence on the proposed intervention is complete (i.e., meeting international standards on reporting) and consistent with the sources cited.

- Relevance and validity of evidence - Extent to which evidence on the proposed intervention is relevant to the decision-making body (in terms of population, disease stage, comparator interventions, outcomes etc.) and valid with respect to international standards (i.e., study design etc.) and conclusions (agreement of results between studies.

Study design & results

- Robust and unbiased estimates - Use of rigorous methodologies and statistical analyses that minimize biases, ensure validity, and provide reliable and credible findings.

By adhering to high reporting standards, stakeholders contribute to the overall integrity and quality of the evaluation process, enabling more accurate and informed decision-making.

8 Evaluation

8.1 Introduction

CHIEF draws on the principles of the EVIDEM [8] and Multi-Criteria Decision Analysis (MCDA) methodology [9] to provide a structured and evidence-based evaluation process.

The integration of EVIDEM and MCDA methodologies enables stakeholders to evaluate solutions based on a range of criteria that is pre-determined through stakeholder engagement, weight their relative importance, and make evidence-based decisions. This provides a structured framework that ensures transparency consistency, and rigor throughout the evaluation process.

The final evaluation techniques used in the CHIEF Framework will be a mixed method approach using a quantitative approach to capture the numerical rating scales along with feedback, suggestions, and opinions of the reviewers on the assigned evaluation panel using free text as a qualitative approach.

Evaluators
It is recommended that stakeholders, including hospital providers, decision-makers, and funders who are considering the investment, adoption, or scale of the solution, participate in the evaluation process facilitated by the framework. Their involvement in the evaluation will ensure that their perspectives and insights are taken into account, leading to more informed and consensus-driven decisions.

8.2 Evaluation Process

Below is a summary of evaluation process -

1. Evaluation goal setting
   The primary goal of evaluation, in the context of CHIEF, is to help stakeholders determine whether the innovation under review should progress to further development, investment, adoption, or scale. The evaluation seeks to provide evidence-based recommendations and insights to stakeholders such as healthcare providers, decision-makers, and funders, who are involved in assessing the value and feasibility of the innovation.

2. Establish the value components considered in decision making
   Evaluators should be involved in the selection of appropriate value components that will be used to evaluate the solution. The value components serve as key criteria against which the innovation's impact and value are measured.

3. Value-System Elicitation (Weights)
   The purpose of this step is to assign weights to the criteria to reflect their relative importance. The weights indicate the priority or significance of each criterion in the evaluation process.

4. Quality of evidence
   This involves evaluating the quality and relevance of available evidence to support decision-making.

5. Criterion scoring and insights
   The solution will be evaluated against each criterion, and scores assigned to reflect its performance capability in relation to each criterion. This will be based on the evidence provided, and the expertise of the evaluators. A comments section will be provided for evaluators to provide feedback to the producers of evidence.

6. Decision
   A simple MCDA linear model will be used to capture the value estimate (V) of the intervention and compared against a scale of 0 to 100%, where 0 is “no go”, and 50% is the minimum value for “go”.

8.3 Decision Appeal

At the conclusion of the evaluation process, solution developers will have the opportunity to review and consider the results of the assessment.

It is important to note that the evaluation outcomes provided by the framework are intended to serve as basis for decision-making and recommendations. As such, solution developers have the right to accept or appeal the results if they believe there are grounds for reconsideration.

If solution developers choose to appeal the evaluation results, they should submit a formal request for review, providing additional supporting evidence or justifications. Appeals should be focused on demonstrating specific concerns or providing new evidence that may have been overlooked or not adequately considered during the initial evaluation.

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9 APPENDIX 1

General considerations in health economics studies

When conducting a health economics study, it is important to consider various factors to ensure a comprehensive and robust analysis. This section provides an overview of general items that should be included in full health economics studies to ensure its methodological rigor and relevance.

1. Measure of the estimated treatment effect (i.e., clinical effect size)

It is important to consider the following factors when estimating the clinical effect size -

- Quality of the evidence based on risk of bias assessment
- Relevance of the evidence: based on the assessment of the similarity between the local healthcare system and where the evidence is generated (e.g., care pathways, setting)
- Comprehensiveness of the evidence: based on whether the estimates are representative of the clinical literature as a whole

The systematic reviews or meta-analysis of high-quality studies are preferred for base-case analysis. However, estimates from a single study may be used in cases where there is sparse clinical literature or where there is only a single high-quality study with significant heterogeneity, that is most generalizable to the local context.

2. Choice of comparators

In health economics evaluation, the appropriate comparator is a therapy or care package (preferably the optimal or gold standard) that is most likely to be displaced by adoption of the new treatment. [1]

Sometimes both the technology and comparator or standard care are part of a sequence in the care pathway. In such cases, the evaluation may compare alternative care pathway sequences.

The choice of comparator(s) should also consider the reference “current care” presently used in Singapore, and the comparators should reflect the target population of interest.

The choice of comparators depends on the specific context, availability of data, clinical guidelines, and the objective of the health economic evaluation. It is necessary to describe the interventions or strategies being compared, as well as explain why they were chosen.

3. Care pathway

The care pathway is an important consideration for evaluating the technologies’ effectiveness and costs. It includes the entire sequence of tests and treatments relevant to the evaluation as well as technologies to help with any adverse effects.

The care pathway can vary depending on the patient's conditions, characteristics, or comorbidities. It includes the stages after diagnosis or treatment.

The treatment pathway or range of treatment pathways must be understood in order to assess the value of the technology.

For diagnostic technology it includes any variations in pathways according to test results or the technologies used. It defines the time frame for the treatments covered, key steps leading to final outcomes, and the outcomes relevant to treatments that will be included in the evaluation. It also covers the diagnostic procedures, treatments, monitoring, retreatment, treatment for adverse effects and complications of the patients.

If a test diagnoses a condition that would not have been diagnosed by the comparator, then the benefits of not having other treatments or tests are relevant. Even if a test diagnoses an untreatable condition, the costs and harms of treatment that can now be avoided are relevant.

4. Clinical Outcomes

An essential step is to identify the key outcome measures relevant to estimate clinical effectiveness, including health benefits and adverse effects that are important to patients and providers.

Clinical outcome measures may also include quantification of survival or health-related quality of life. These measures are often combined to calculate a summary measured as quality-adjusted life-years (QALYs) to evaluate cost-effectiveness.

The accuracy of outcome measurement is crucial for obtaining reliable and valid results using standardized clinical criteria that involve the use of established guidelines or criteria for diagnosis, classification, or assessment of specific conditions or clinical outcomes; standardized outcome definitions that provide clear and consistent descriptions of the outcomes being measured; and laboratory tests.

It is important to conduct Event adjudication activities carried out by the independent event adjudication team to ensure the accurate, reliability, objectivity, and standardization of event assessment as well as unbiased assessment of clinical events or outcomes.

Patient-reported outcome measures can capture important aspects of disease conditions and interventions, such as health-related quality of life, performance status, symptom and symptom burden, and health-related behaviours such as anxiety and depression. They can be either general or disease specific.

A high-quality “Core Outcome Set (COS)” should be implemented, developed by the Standards for Development (core outcome sets-STAD) and Core Outcome Set Standards for Reporting (core outcome sets-STAR). This is to ensure standardization and harmonization of the outcome measured and reported in clinical trials and research studies, thus reducing selective outcome reporting, and increasing the relevance of results. [5]

5. Estimate of Clinical Effectiveness

If the estimate of clinical effectiveness is based on Single study-based effectiveness estimates, it is important to fully describe the design features of the single effectiveness study and justify why it is a sufficient source of clinical effectiveness data.

If the estimate of clinical effectiveness is based on Synthesis-based estimates, a description of the methods used for identification of included studies and synthesis of clinical effectiveness data should be provided.

6. Assessment of data quality, validity, robustness, and generalizability

It is important to note that data on treatment effectiveness as well as clinical outcome(s) estimates should be based on robust clinical trials or observational studies.

It is important to assess the quality, accuracy, consistency, and validity of the data used, as well as the generalizability of the results to the target population. [3]

7. Currency, price date, and conversion

It is important to consider factors such as currency, price date, conversions, and the following adjustment factors to ensure accurate and meaningful comparisons in the cost analysis -

- dates of the estimated resource quantities and unit costs.
- methods for adjusting estimated unit costs to the year of reported costs if necessary.
- methods for converting costs into a common currency base and the exchange rate.

8. Perspectives

A healthcare payer perspective, which takes into account hospitals and patients, will be considered as the evaluation and adoption of the proposed technology will occur primarily in hospitals, including primary healthcare and community hospitals.

Health care sector perspective: A viewpoint for conducting a cost-effectiveness analysis that includes formal health care sector (medical) costs borne by third-party payers and paid out-of-pocket by patients. These third-party and out-of-pocket medical costs include current and future costs that may or may not be related to the condition under consideration. [6]

Patient perspective: Health economic analysis from the patient perspective focuses on assessing the cost-effectiveness and value of health care interventions or treatments from the patient's point of view. It takes into account both the economic impact and the patient's experience, preferences, and quality of life. [4]

9. Time Horizon

In the reference case, the time horizon should be long enough to capture all relevant differences in future costs and outcomes associated with the interventions being compared.

Thus, the time horizon should be based on the condition and the likely impact of the intervention. The time horizon of the evaluation should relate directly to the decision problem.

10. Discounting

In the reference case, costs and outcomes that occur beyond one year should be discounted to present values at a rate of 1.5% per year. [2]

The impact of uncertainty in the discount rate should be assessed by comparing the results of the reference case to those from non-reference case analyses, using discount rates of 0% and 3% per year.

11. Choice of model and model assumption

The description of the model and the rationale for selecting the specific type of decision analytical model used, as well as model assumptions, should all be described and illustrated.

12. Characterizing uncertainty

Single study-based economic evaluation

Uncertainty is a common challenge in single study-based economic evaluations. One important aspect to consider is the effect of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).

Model-based economic evaluation

Uncertainty is also a crucial factor to consider when conducting model-based economic evaluations. It is essential to describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.

13. Characterizing heterogeneity

It is important to identify and report any differences in costs, outcomes, or cost-effectiveness that can be attributed to these effects of variations due to heterogeneity. Heterogeneity could be explained by variations between subgroups of patients with different baseline characteristics, or other observed variability in risk profiles of the patients that could contribute differences in clinical effects (health outcomes).

Reporting the effect of heterogeneity in costs and outcomes between subgroups of patients can help decision makers to make informed choices about which treatment options are most appropriate for different patient populations.

14. Cost categories

The cost of implementing healthcare technology in a hospital may vary depending on the type, size, scope, and other factors.

(1) Direct costs
- Expenses directly associated with the delivery of a health care service. In the context of a hospital, direct costs may include expenses for patient care and treatment.
- Expenses directly related to medical care provided to patients. These costs can be incurred by patients, insurers, or healthcare providers.

(2) Direct costs to the patients
- Expenses that patients may incur directly as a result of seeking medical care.
- The specific direct costs to patients may vary widely depending on the type and severity of the medical condition, the type of medical care needed, and other factors.

(3) Indirect Medical costs:
- Expenses that are NOT directly related to medical care but may result from a medical condition or treatment.
- Specific indirect costs associated with health care can vary widely depending on the type and size of the health care facility, the extent of services provided, and other factors.

(4) Indirect costs to the patients:
- Expenses that are not directly related to the medical treatment itself may incur as a result of seeking medical care.

- These specific indirect costs to patients can vary widely depending on the type and severity of the medical condition, the type of medical care needed, and other factors.

15. Evidence on resource use and costs

Depending on the perspective of the analysis and the indication of the technology, the resource use and associated costs need to be taken into account based on available evidence, and data on resource use and costs need to be identified systematically.

The utilization of technology and resources as well as associated costs should include costs of the technology, the related procedures, monitoring, treatment-related adverse events, and disease progression.

In addition, estimates of resource use should include the comparative costs or saving of the technologies and changes in infrastructure, utilization, and maintenance, including the comparative value of healthcare utilization outcomes (such as length of hospital stay, number of hospitalizations, outpatient, or primary care consultations) associated with the technology or its comparators.

Staff training costs should also be included (if applicable).

Reference-case analyses should be based on prices that reflect as closely as possible the prices paid at local hospitals and follow standard MOH guidelines for all evaluations.

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