TOOL FOR EVIDENCE GENERATION

for collaborations between MedTech companies, innovators and researchers.
Click the information icons (i) throughout the diagram for additional details.
Use the arrow symbols throughout the material to return to this view.

Version: 2023-08-18 EN

Start here.

Beyond CE marking, is there evidence for efficacy and safety

Yes

No

STRATEGY FOR EVIDENCE EVALUATION

Evidence is generated through any of the following designs:
- Randomised controlled trial
- Cohort trial
- Case series with sufficient sample size

No

Yes

Reported study outcomes include any of the following:
- Clinical measurements of outcome(s)
- Health economic measure(s)
- Organisational measure(s)
- Patient ethics measure(s)

If more than one study:
- Comparable outcomes across studies

No

Yes

Do studies support each other?

Yes

No

Studies are clearly defined with regards to:
- Patient/study population
- Intervention
- Control group
- Measurement(s) of outcome

If more than one study:
- Comparable outcomes across studies

No

Yes

Do studies support each other?

Yes

No

Measurements of outcome include any of the following:
- Intermediary measurements of outcome
- Clinical measurements of outcome
- Outcomes can be linked to health economics

If more than one study:
- Comparable outcomes across studies

No

Yes

Information on the Health Technology Assessment (HTA) process

STRATEGY FOR EVIDENCE GENERATION

Specify intended use, patient group and treatment area. Define patient/user involvement.

Financing and budget.

Establish contact with clinical stakeholders. Identify relevant clinical centres for conducting the study.

Setup agreement with academics and clinicians.

Identify gold standard control/ comparable technologies and their usage.

Formulate study research question.

Identify intermediary and clinical outcome measures. Health economy, organisation, patient ethics.

Are measurement techniques validated?

No

Yes

Validate measurement techniques OR chose other techniques.

Study design according to evidence grade and feasibility.

Expected effect size(s) and estimated number of study participants.

Do centres meet recruitment requirements?

No

Yes

Establish contact with additional clinical centres.

Regulatory requirements and quality management.

Create plan for data documentation tools and analysis.

Ethics application and evaluation.

Conduct study.

Back to start.

» Beyond CE-Marking, Is There Evidence for Efficacy and Safety?

Summary

- Evidence includes data generated for the developed product, or published data for similar or comparable products.
- Ensure that a publication strategy is in place.
- Register studies through the open databases.

☐ Completed.

Notes:

Add notes here.

Evidence for Efficacy and Safety

Evidence should include data generated for the developed product and from the peer-reviewed literature for similar products. Health technology assessment (HTA) conducted by the regional HTA units are mainly based on published peer-reviewed studies. However, both the TLV (the Dental and Pharmaceutical Benefits Agency) and the regional HTA units consider unpublished evidence produced by the manufacturer. Early consideration of publication strategy is of value in anticipation of future assessment. The figure below shows the most commonly used databases for searching for evidence in regional HTA reports. Assessors also consider ongoing studies as identified through, *e.g.*, ClinicalTrials.gov or World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP).

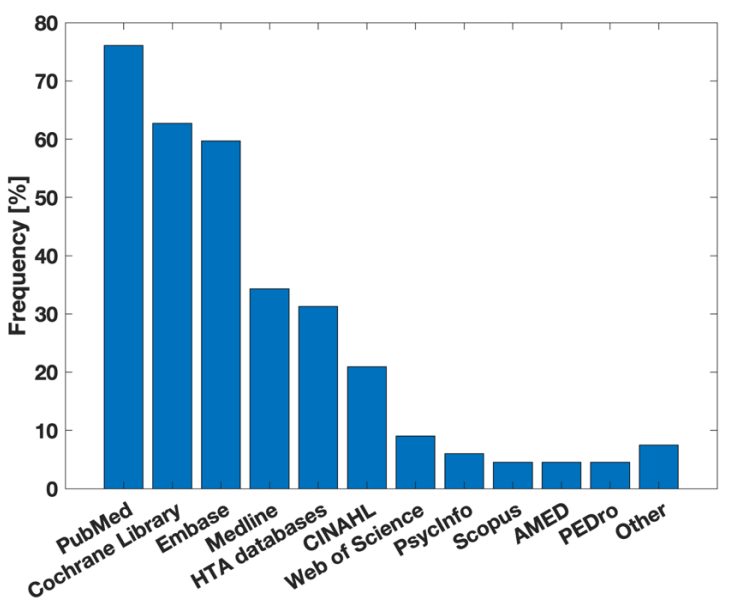

Figure. Most utilised databases for searching for evidence as reported in the regional HTA reports (published 2016 - 2021).

Read more about publication strategy and registration of clinical trials

- **Clinical Studies Sweden.** Publication. https://kliniskastudier.se/english/research-process/publication
- **ClinicalTrials.gov.** https://clinicaltrials.gov
- **WHO.** International Clinical Trials Registry Platform. https://www.who.int/clinical-trials-registry-platform

» A. Regarding Study Design, How Is Evidence Graded?

Summary

- During health technology assessment (HTA), evidence is usually graded, and selected, according to criteria based on the Cochrane pyramid.
- Information on evidence grading and previously published HTA reports can be useful in guiding clinical study design.

☐ Completed.

Notes:

Add notes here.

How is Evidence Generated?

According to SBU's Method Book, evidence is graded according to the Cochrane pyramid, among others. This is also reflected in the inclusion and exclusion criteria for data collection during regional HTA. Commonly included study designs are systematic reviews, randomised controlled trials, non-randomised controlled studies, cohort studies and case series. Healthcare registry data has also been used more recently. In many cases the minimum number of study participants is also stated. This varies between five and 5,000 individuals, or a median of approximately 20 study participants per study or study arm depending on the study design.

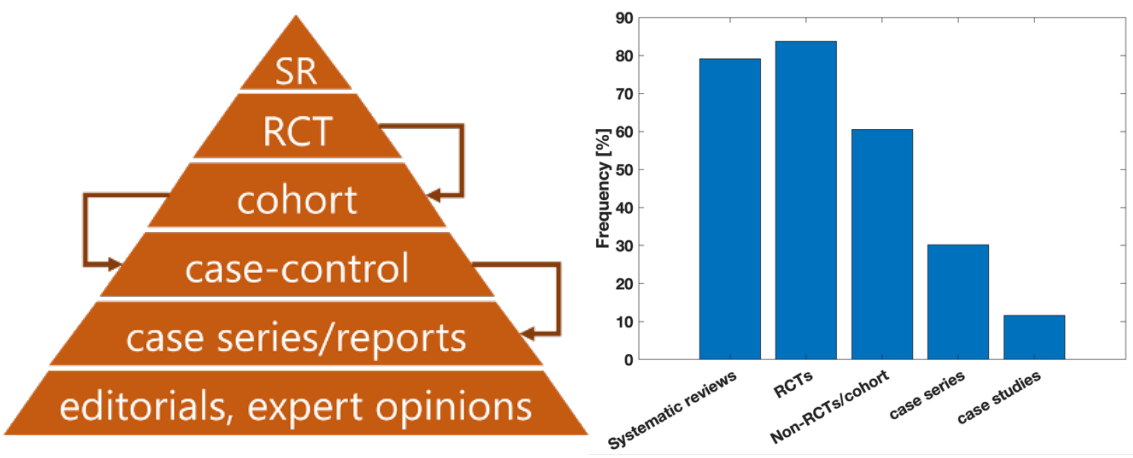

Figure. *Left*: The Cochrane pyramid for evidence grading. *Right*: Frequencies of types of included study designs in regional HTA reports.

Reasons for Excluding Study Data

The figure shows the most common reasons for excluding study data during HTA. These include instances where the PICO (patient, intervention, control, outcome) does not correspond to the defined PICO in the overall aim of the HTA report. Other common reasons for exclusion of evidence include the wrong type of study design, wrong publication type, low study quality and too few study participants. The category 'other' mainly includes studies where the data of interest could not be extracted from the study for the purpose of comparing study groups or interventions, or meta-analysis.

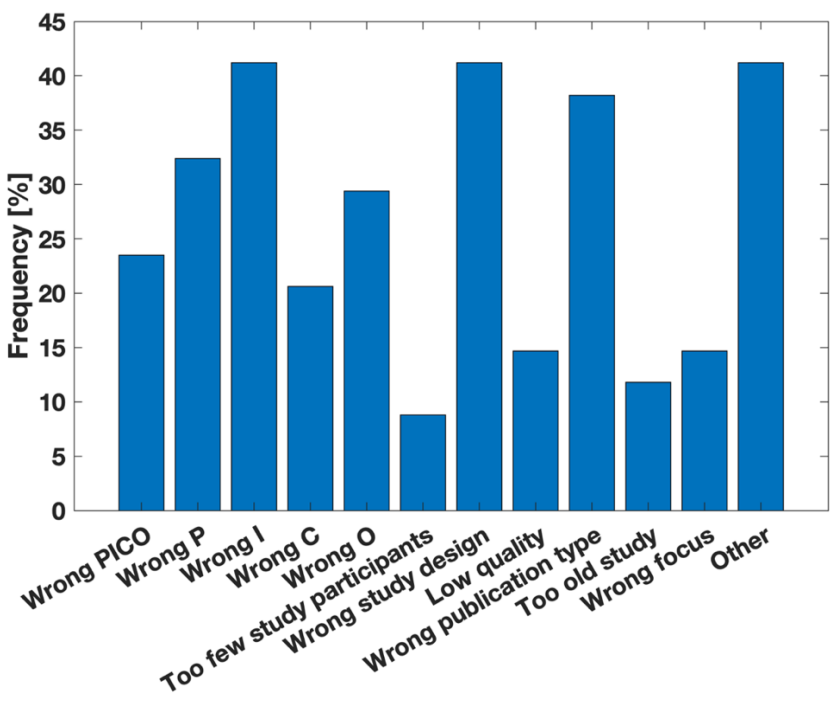

Figure. Most common reasons for excluding study data during HTA.

The Database

A database was collated of analysed HTA reports. The database contains summarised information from over 60 HTA reports published during 2016-2021. In the database, it is possible to search for summary information from reports. The table below shows an example of an extract of the collected data, with the report title, inclusion criteria, reasons for excluding study data, and link to reference.

Table. Example of extracted information on excluded data from the HTA analysis database.

Title	Selection, relevance	Excluded publications
MRI-Guided Radiotherapy in Patients with Cancer in Thorax, Abdomen, Pelvis or Head and Neck	Eligibility criteria: study design: systematic reviews, randomised controlled trials, non-randomised controlled trials, case series if over or equal to five patients. Language: English, Swedish, Norwegian, Danish. Publication data: 2010 - present.	Number of publications excluded: 39. Reasons for exclusion - Wrong I: only plan no treatment, no MR-linac, gating system, no MR-linac exposure; Wrong O: physician rated visibility, recording of organ motion; Other: Case series with limited information/patient number, wrong publication type, no treatment, method development, wrong study design.

Selected References and Recommended Reading

- **SBU's Method Book.** Evidence grading in HTA, Section 9. https://www.sbu.se/sv/metod/sbus-metodbok/?pub=48286&lang=sv
- **EUnetHTA.** Evidence generation. https://www.eunethta.eu/grade/

» B. Relevant Study Outcomes

Summary

- Health technology assessment (HTA) is carried out based on defined clinical research questions, health economics, organisation and patient ethics.
- Information on evidence grading and previously published HTA reports can be useful for ideation and verification during clinical study design in anticipation of HTA.

☐ Completed.

Notes:

Add notes here.

Clinical Research Questions

During HTA, medical technologies are evaluated based on a set of questions across the categories: clinical research question, health economics, organisation and patient ethics. The figure below shows the most common elements in the structure of clinical research questions for HTA. These often focus on treatment specific outcome measures, a technology or method, comparator, and relevant patient group. This may be of use when designing research questions in clinical studies.

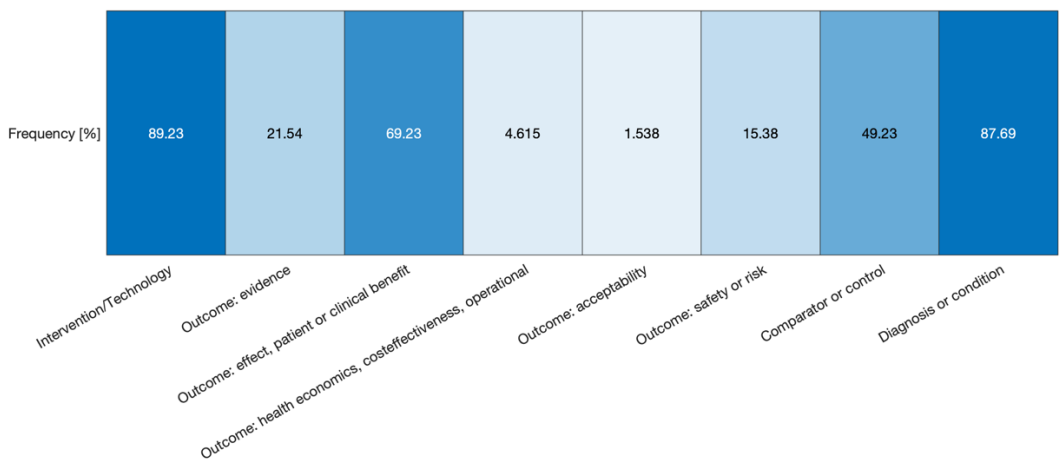

Figure. Prevalence of elements in defined clinical research questions for HTA.

Themes and Aspects Considered During HTA

The network map (developed using kumu.io) below gives a summary of themes and aspects considered during health economic evaluation, organisational assessment and patient ethical analysis during HTA. This based on thematised data from 66 HTA reports published during 2016-2021.

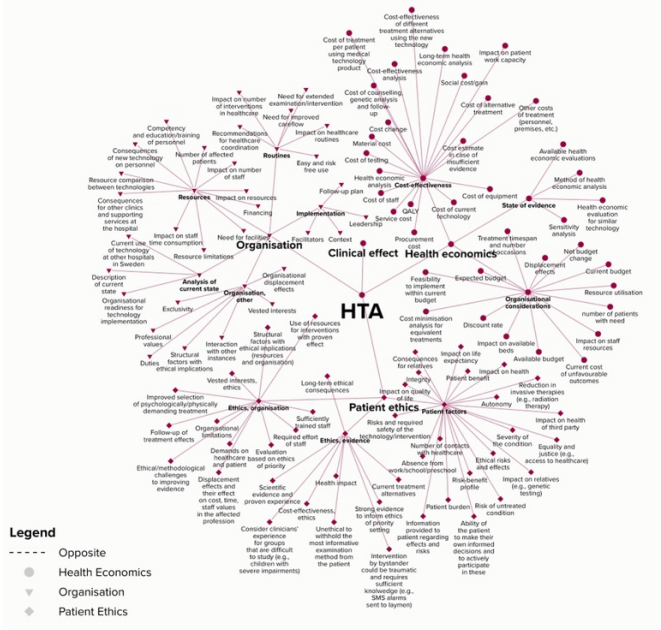

Figure. Themes and aspects considered during HTA.

Link to original view in Kumu: https://embed.kumu.io/d9aa4c7399f2c0c83cc7effa71bc6c22

Link to interactive presentation in Kumu: https://adamdarwich.kumu.io/aspects-conisdered-during-health-technology-assessment-hta-in-sweden

The Database

The data analysis database contains summary information from 66 regional HTA reports published between 2016 and 2021. The database is searchable and allows retrieval of information on, for example: clinical research questions, evaluations on health economics, organisational factors and patient ethics. The table below illustrates an example of the type of information that can be retrieved related to the above aspects.

Table. Example of extracted information on research questions from the HTA analysis database (note: translated from Swedish).

Title	Clinical research question	Organisation	Health economics	Patient ethics
Ultrasound for acute scrotal symptoms –can the number of scrotal explorations be reduced? [*Ultraljud vid akuta skrotala symptom –kan antalet skrotala explorationer minska?*]	Can the number of scrotal explorations for patients with acute scrotal symptoms by reduced without increasing the number of missed testicle torsions if the clinical examination is supplemented with ultrasound of the scrotum?	Interaction with functions: requires new routines in acute care; requires more ultrasound resources; the number of acute explorations are anticipated to reduce; additional training required; mainly affects acute care. Implementation: requires adapted routines; involved leadership; facilitators –all affected in the unit; follow-up plan: currently not in place, proposal exists.	Increased number of ultrasound scans, reduced number of explorative operations. Limited increase in cost with possibility for savings due to reduced number of surgeries. No cost-effectiveness analysis available.	Ethical risks and effects: Missed testicle torsion is not acceptable; sedation as associated with risks; shift time is costly; requires more ultrasound staff; if safer diagnostics exist that do not require sedation these should be considered.

Selected References and Recommended Reading

- **SBU's Method Book.** Evidence grading in HTA, Section 9. https://www.sbu.se/sv/metod/sbus-metodbok/?pub=48286&lang=sv
- **EUnetHTA.** Evidence generation. https://www.eunethta.eu/grade/

» C. PICO: Patient Group, Intervention, Control and Outcome

Summary

- PICO is a widely used method for the design of systematic literature reviews.
- Here, PICO may be of use when reviewing your study data to ensure comparability between studies.

☐ Completed.

Notes:

Add notes here.

PICO

PICO is widely a used method to define:

- Patient group or population,
- Intervention,
- Control group, and,
- Measurements of outcome,

for clinical research questions *e.g.*, for health technology assessment (HTA). This is used to aid the selection of study data. The Figure below shows the most common reasons for excluding study data during HTA. PICO can be a useful method for the review of study data and to ensure that studies are comparable.

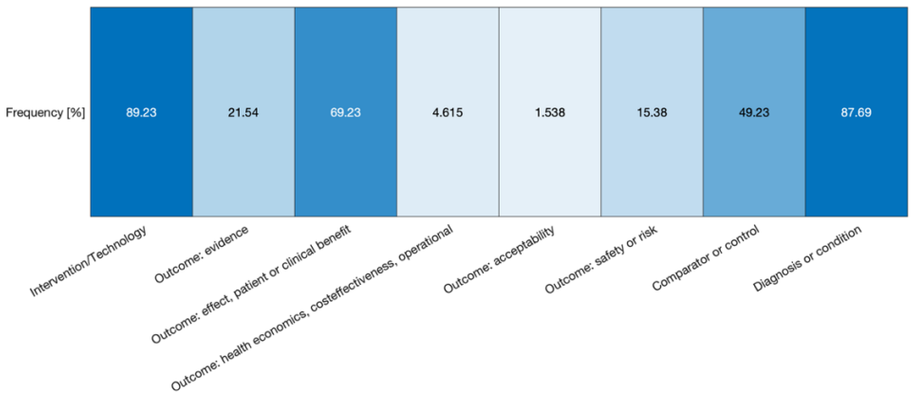

Figure. Frequencies of reasons for excluding study data during HTA.

The Database

The HTA analysis database contains summary information from 66 regional HTA reports published during 2016-2021. In the database, it is possible to search information on PICO. The table below illustrates an example of summary data on PICO.

Table. Example of extracted information on PICO from the HTA analysis database (note: translated from Swedish).

Title	P: patient/population	I: intervention	C: control	O: outcome
Artroscopic decompression for subacromial pain syndrome [*Atroscopic decompression for subacromial pain syndrome*]	Adult (≥18 years-old) patients suffering from long-term (≥6 months) subacromial pain syndrome.P1: Persisting following ≥3 months of physiotherapy (all varieties). P2: Persisting following ≥3 months of other non-surgical therapy, w/wo concurrent physiotherapy. Selection based on national medical indications for shoulder surgery.	ASD w/wo lateral clavicle resection.	Non-surgical treatment.C1: Physiotherapy (all varieties) w/wo surgical treatment. C2: Other specified treatment w/wo physiotherapy.	O1: function, mobility, strength with a number of functional effect indicators. O2: Pain. O3: Health-related quality of life. O4: sick leave, return to normal activity. O5: Secondary surgery due to: O5a: All reasons, O5b: Defined reason. O6: Mortality at 30 days, 1 year. O7: Morbidity; specified: infection, sensory loss, pneumonia, and more. O8: Morbidity: unspecified. Prioritised measurements of outcome: function, pain, health-related quality of life, adverse events.

Selected References and Recommended Reading

- **SBU's Method Book.** Section 3, information on PICO. https://www.sbu.se/sv/metod/sbus-metodbok/?pub=48286
- **EUnetHTA.** Information on PICO. https://www.eunethta.eu/pico/

» D. Measurements of Outcome

Summary

- Defining measurements of outcome is an important step in study design.
- Here we provide resources to inform the ideation and design of measurements of outcome.

☐ Completed.

Notes:

Add notes here.

During HTA, measurements of outcome of interest are identified. These could be categorised as: critical or important for decision-making, intermediary outcomes, or less important for decision-making.

The measurements of outcome are typically highly specific to the treatment area and intervention. However, to exemplify, critical outcomes could include aspects, such as: survival, health-related quality of life, or serious adverse effects. Less important outcome measures could include, *e.g.*, less severe adverse effects.

The Database

The HTA analysis database contains summary information from over 60 regional HTA reports published during 2016-2021. In the database it is possible to retrieve information on assessed measurement of outcome in these HTA reports. An example is given in the table below.

Table. Example search result on measurements of outcome from the HTA analysis database (note: translated from Swedish).

Title	O: outcome
Subcutaneous implantable cardioverter defibrillator [*Subkutan implanterbar kardioverterdefibrillator*]	Total survival, arrythmia free survival. Frequency of correct/incorrect defibrillations, pharmacological/surgical corrections/explantationsdue to device-related complications, battery life, health economic, ethical and administrative/organisational apsects.

Read More About Measurements of Outcome

- **SBU's Method Book.** Section 3, information on PICO. https://www.sbu.se/sv/metod/sbus-metodbok/?pub=48286
- **EUnetHTA.** Information on PICO. https://www.eunethta.eu/pico/
- **SBU – COS. Core Outcome Sets.** https://www.sbu.se/en/about-sbu/cos/
- **ECRIN – The European Outcome-Measure Database.** https://ecrin.org
- **COMET – Core Outcome Measures in Effectiveness Trials Initiative.** https://www.comet-initiative.org/Studies

Summary

- This section provides information on the Swedish health technology assessment (HTA) system and processes for initiating, performing and reporting on HTA.
- The information may be of use for gaining understanding of the Swedish HTA system and how a HTA process is initiated.

Notes:

Add notes here.

Key Actors in the Swedish Health Technology Assessment (HTA) System

The figure below details the key actors in the Swedish HTA system. An interactive version of the systems map can be viewed using the weblink to Kumu in the figure legend. The Kumu map is interactive and allows the selection of individual key actors to access more information and links to additional resources. Here follows a short summary of the system.

Central to HTA, are the regional HTA organisations. These are linked to the healthcare organisations in the regions. Regional HTA centres and regions are represented of the HTA Network, chaired by SBU (The Swedish Agency for Health Technology Assessment and Assessment of Social Services). The aim of the network is to prevent redundant assessments, harmonise methods, and develop new methodologies. SBU carries out independent assessments of methods and interventions in healthcare, among others. The agency also develops the Method Book for systematic reviews and assessments, used by the regional HTA organisations for assessments of medical devices.

TLV (The Dental and Pharmaceutical Benefits Agency) decides on what medicinal products, medical devices and dental care products should be susidised by the state. They also prepare health economic evaluations of evidence on medical devices for decision-making in the healthcare regions.

The MTP (Medical Technology Product) Council has the mandate to issue recommendations on the usage of some new medical devices.

For more information on the system and actors, please see the link Kumu map.

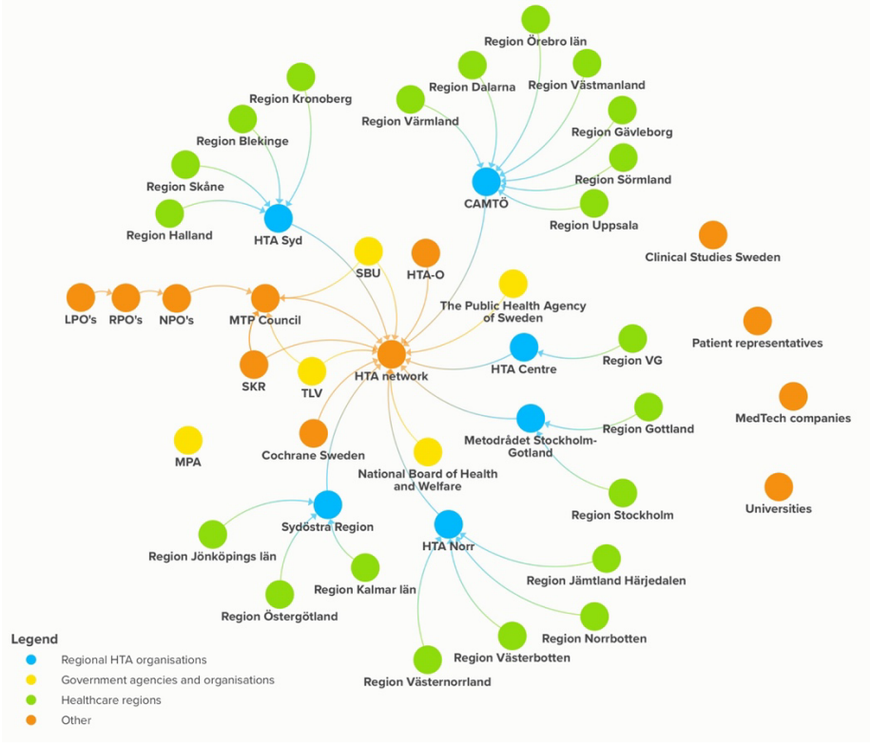

Figure. Key actors and their connections in the Swedish HTA system.
Link to original view in Kumu:
https://embed.kumu.io/4a71e0b9942fa9c8bec97c6bd5970817

See the next page for information on the HTA process

Health Technology Assessment (HTA) Process Map

The figure below gives a summary overview of the HTA process; including how the process is initiated, carried out (in general steps) and what the process outcomes are.

HTA can be initiated via several routes, the most common one being through a direct request to a regional HTA organisation from management, specialist consultants or other professionals in the healthcare organisation. Regional HTA is then carried out (see the blue box in the figure below). An assessment report is produced and delivered to the healthcare organisation for decision making. Depending on the state of evidence a mini-HTA may be produced.

HTA can also be initiated through the MTP (Medical Technology Products) Council, where questions are brought by the MTP member organisations (such as, the National, Regional and Local Programme Areas). If an assessment of evidence is available, the evidence will be evaluated to produce a statement of recommendation (see the orange box in the figure below). If no assessment of evidence has been carried out the MTP Council can request one to be carried out, either by a regional HTA organisation or the TLV (the Dental and Pharmaceutical Benefits Agency).

Medical device manufacturers can request a HTA by contacting TLV directly. TLV will produce a health economic evaluation (see the yellow box in the figure below) as basis for decision-making in the regional healthcare organisations or at the MTP council.

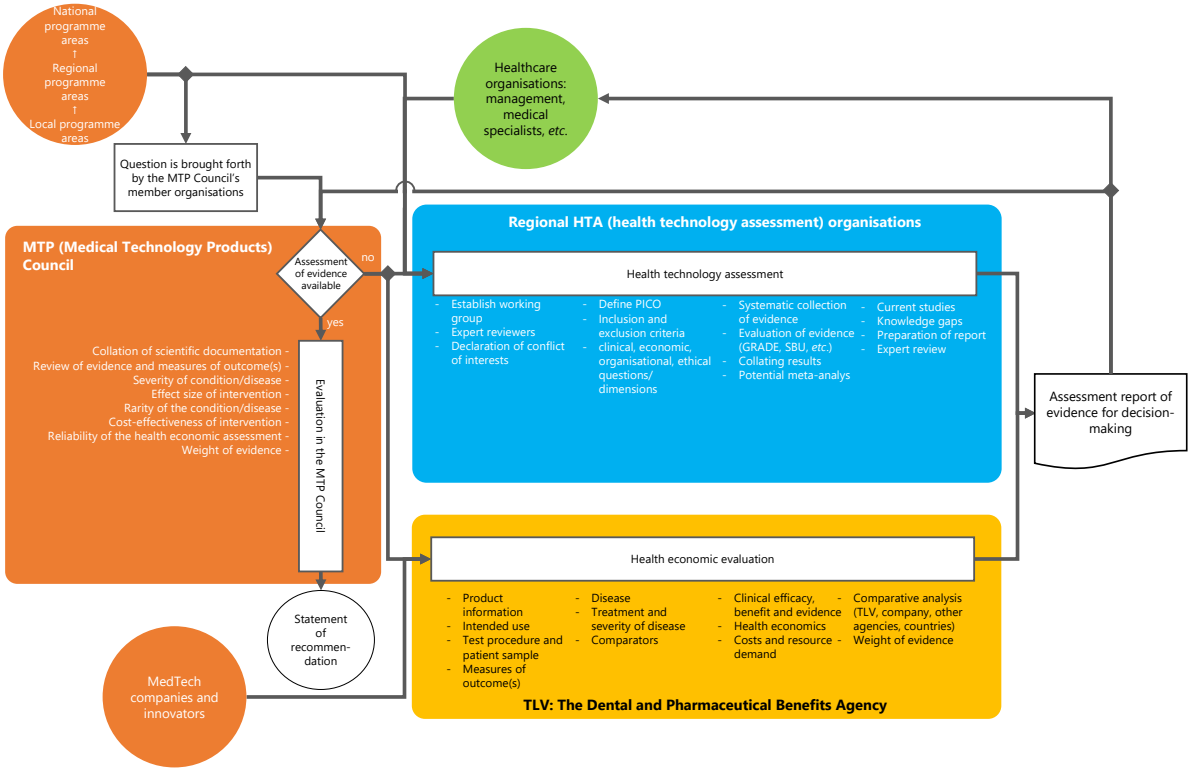

Figure. Summary overview of the HTA process map.

» Indication, Patient Group, Involvement, and Treatment Area

☐ Completed.

Notes:

Add notes here.

Here is presented several weblinks with relevant information on defining the intended use, patient group, treatment area and patient/user involvement. An important need that was highlighted by experts during the development of this tool was the lack of early patient and/or user involvement, as well as the need for inclusive innovation and user design in medical device development.

- **SBU.** Method Book, Section 3. https://www.sbu.se/sv/metod/sbus-metodbok/?pub=4828
- **Clinical Studies Sweden.** Idea – specific rules for medical devices. https://kliniskastudier.se/english/research-process/idea#h-Specificrulesformedicinalproductsormedicaldevices
- **FORMAS.** Inclusive research and innovation. https://formas.se/analys-och-resultat/publikationer/2018-12-23-inkluderande-forskning-och-innovation.html
- **Medtech4Health.** Inclusive design handbook. https://medtech4health.se/projektportfolj/strategiska-projekt/inkluderande-innovation/
- **FASS.** List of patient organisations in Sweden. https://www.fass.se/LIF/patientorganisations

» Financing and Budget

☐ Completed.

Notes:

Add notes here.

Here is given a weblink with information on financing and budget.

- **Clinical Studies Sweden.** Planning – Study budget. https://kliniskastudier.se/english/research-process/planning#h-Studybudgetforallthecostsintheproject

» Establish Contact with Clinical Stakeholders and Centres

☐ Completed.

Notes:

Add notes here.

Establishing contact with clinical stakeholders and identifying relevant centres for trials is a common hurdle to evidence generation for medical devices. Clinical Studies Sweden hosts a service for submitting direct requests to healthcare organisations.

- **Clinical Studies Sweden.** Feasibility Process. https://feasibility.kliniskastudier.se/english.html

» Agreements with academic partners and clinicians

☐ Completed.

Notes:

Add notes here.

Here is given a weblink with a guide on agreement and budget for collaborative clinical study projects.

- Clinical Studies Sweden. Planning – Agreement and budget in clinical studies. https://kliniskastudier.se/english/research-support/agreement-and-budget

» Gold-Standard Control and Comparable Technologies

☐ Completed.

Notes:

Add notes here.

Identifying the right gold-standard control, or comparable technology and its use, is an important enabler for inclusion of data in later evaluation of evidence. More information on this is available through the weblinks below.

- **SBU.** Method Book, Section 3. https://kliniskastudier.se/english/research-support/agreement-and-budget
- **Clinical Studies Sweden.** Idea. https://kliniskastudier.se/english/research-process/idea
- **EUnetHTA.** Evidence Submission template. https://www.eunethta.eu/ja3services/submission-guidelines/submission-template-pharmaceuticals-submission-template-medical-devices/

» Formulate Study Research Question

☐ Completed.

Notes:

Add notes here.

The weblinks below provide some information on how study research questions can be defined.

- **SBU.** Method Book, Section 3. https://kliniskastudier.se/english/research-support/agreement-and-budget
- **Clinical Studies Sweden.** Idea. https://kliniskastudier.se/english/research-process/idea

» Identifying Measurements of Clinical Outcome, Health Economics, Organisation and Patient Ethics

☐ Completed.

Notes:

Add notes here.

The weblinks below provide information on how measurements of outcome are evaluated and input on how these can be defined. In addition, more information is available in this tool, here.

- **SBU.** Method Book, Sections 3, 12 & 13. https://kliniskastudier.se/english/research-support/agreement-and-budget
- SBU. COS: Core Outcome Sets. https://www.sbu.se/en/about-sbu/cos/
- **TLV.** Health Economic Evaluations of medical devices. https://www.tlv.se/in-english/medical-devices/health-economic-evaluations.html
- **ECRIN.** The European Outcome-Measure Database. http://outcome-measure.ecrin.org/
- **COMET.** Core Outcome Measures in Effective Trials Initiative. http://comet-initiative.org/

Summary

- Clinical study design is challenging for medical devices. This section introduces some of the common challenges and solutions to overcome these. We link to additional resources on evidence grading and clinical study design.
- The section can be used as a starting point to explore and plan clinical studies for medical devices.

☐ Completed.

Notes:

Add notes here.

Evidence Grading

According to SBU's Method Book, evidence is graded according to the Cochrane pyramid, among others[1]. The most common included study designs are systematic reviews, randomised controlled trials, non-randomised controlled studies, cohort studies and case series. Healthcare registry data has also been used. In may cases the minimum number of study participants is also stated. This varies between five and 5 000 subjects, or a median of approximately 20 study participants per study or study arm depending on the type of study.

The following material present some of the medical device-specific challenges to clinical trial design and strategies for overcoming these.

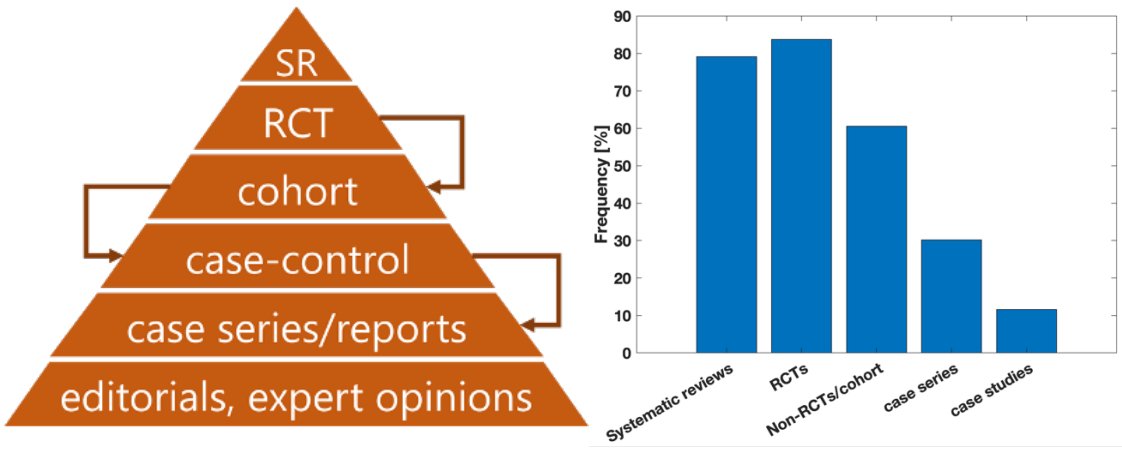

Figure. *Left*: The Cochrane pyramid for evidence grading. *Right*: Frequencies of included study designs during health technology assessment.

[1]SBU Method Book – Read more on evidence grading at: https://www.sbu.se/sv/metod/sbus-metodbok/?pub=48286&lang=sv

The IDEAL Framework (by Mulloch *et al.*, 2013)

The figure below presents the IDEAL framework. The model was developed by a consortium of experts to provide guidelines on what type of studies to carry out when in the development cycle of surgical techniques and medical devices to meet the regulatory requirements (See Figure below). The proposed framework provides several learnings for medical devices and evidence generation. To learn more, please review the original research publications and resources cited below.

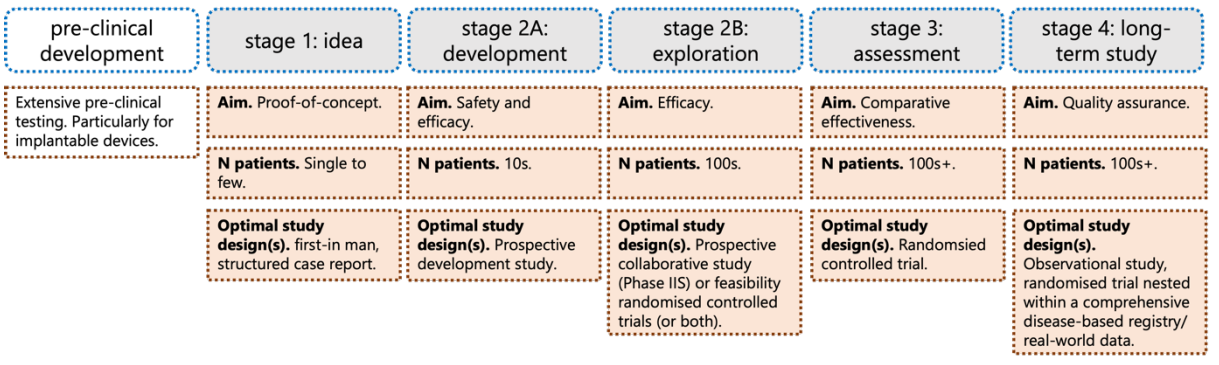

Figure. IDEAL framework (adapted from Mulloch *et al.*, 2013).

Key Challenges to Clinical Trial Design

The Figure below highlights and explain some of the key challenges to clinical trial design for medical devices.

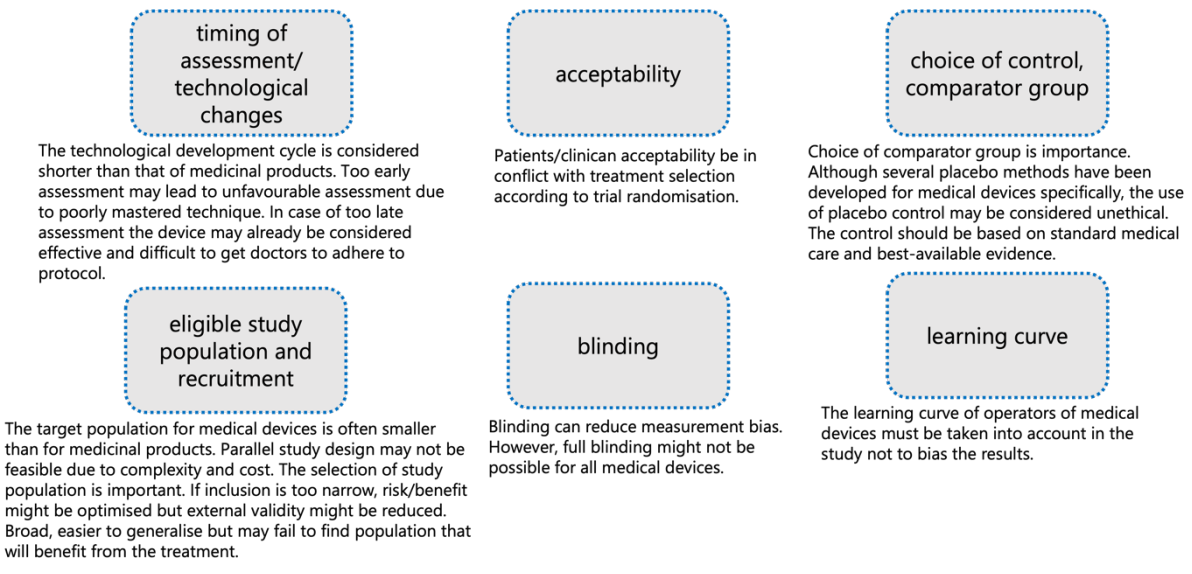

Figure. Medical-device specific challenges in clinical trial design (adapted from Bernard, et al., 2014 and Neugebauer et al., 2017).

See the next page for information on strategies for trial design ← →

Suggested Solutions

Strategies for overcoming the above challenges are given in the figure below.

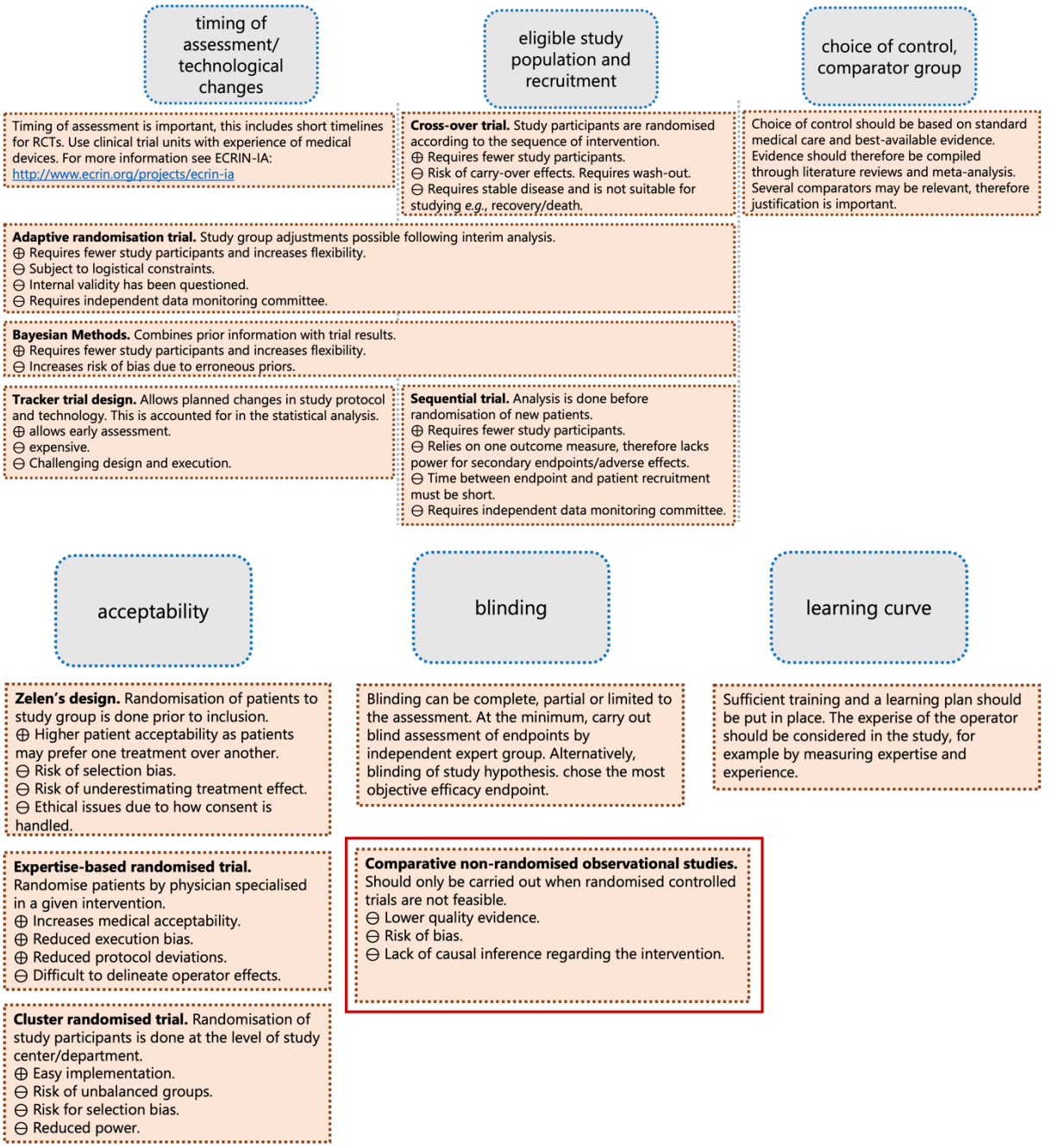

Figure. Medical device-specific challenges and strategies to overcome these in clinical trial design (adapted from Bernard, *et al.*, 2014 and Neugebauer *et al.*, 2017).

Selected References and Additional Information

- SBU. Method Book, Sections 3 on evidence grading. https://www.sbu.se/sv/metod/sbus-metodbok/?pub=48286&lang=sv
  The IDEAL Framework. Publications and resources.
- Mulloch, *et al.* BMJ 2013;346:f3012 doi: https://doi.org/10.1136/bmj.f3012
- Sedrakyan, *et al.* BMJ 2016;353:i2372 doi: https://doi.org/10.1136/bmj.i2372
- Fleetcroft, et al. BMJ Surg Interv Health Technologies 2021;3:e000066 doi: https://doi.org/10.1136/bmjsit-2020-000066
- IDEAL website: http://www.ideal-collaboration.net/
  More information on study design for medical devices:
- Bernard, *et al.* Medical Devices: Evidence and Research 2014;7:325-334 doi: https://dx.doi.org/10.2147/MDER.S63869
- Neugebauer, *et al.* Trials 2017;18:427 doi: https://doi.org/10.1186/s13063-017-2168-0
- ECRIN. European research infrastructure. https://ecrin.org

» Establish Contact with Additional Clinical Collaborators

☐ Completed.

Notes:

Add notes here.

The number of study participants is an important factor in the evaluation of reliability of clinical data. Here is given a weblink to resources on coordinated clinical study requests and clinic requests.

- **Clinical Studies Sweden.** Feasibility Process
  https://feasibility.kliniskastudier.se

» Regulatory Requirements and Quality Management

☐ Completed.

Notes:

Add notes here.

The Swedish Medical Products Agency provides resources and guides for meeting the regulatory requirements, according to the Medical Devices Regulations. A weblink is given below.

- **Medical Products Agency.** Planning, Analysis and Publication. https://www.lakemedelsverket.se/en/permission-approval-and-control/clinical-trials/medical-devices/clinical-investigation-of-medical-device/application-and-notification-mdr

» Plan Data Collection Tools and Analysis

☐ Completed.

Notes:

Add notes here.

Here is given information on data collection and statistical analysis strategy. Relevant tot this is also to establish a publication strategy for dissemination of clinical research findings.

- **Clinical Studies Sweden.** Planning, Analysis and Publication. https://www.kliniskastudier.se/english/research-process/planning

» Ethics Application and Evaluation

☐ Completed.

Notes:

Add notes here.

For medical devices, ethics applications should be submitted to the Swedish Medical Products Agency. Weblinks to information resources follow below.

- **Medical Products Agency.** Medical devices, application. https://www.lakemedelsverket.se/en/permission-approval-and-control/clinical-trials/medical-devices/clinical-investigation-of-medical-device/application-and-notification-mdr
- **The Swedish Ethical Review Authority.** Information on medical devices. https://etikprovningsmyndigheten.se/medicintekniska-produkter/
- **Clinical Studies Sweden.** Information on ethics application. https://kliniskastudier.se/english/research-process/application