Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

Guidance notes for completing KCE Trials application from

Refers to Application Form v1.0 – 30/05/2018

Contents

KCE TRIALS PROGRAMME

PART 1: GENERAL INFORMATION

KCE Trials programme

Many research questions in healthcare are currently not sufficiently studied using clinical trials, despite their high societal importance. The KCE Trials programme is a programme of pragmatic practice-oriented clinical trials funded by KCE to support better patient care and to ensure a more efficient use of public resources (https://www.kce.fgov.be/en/content/what-is-kce-trials).

These notes are intended to support candidate investigators and sponsors to provide the required information within the "Research Outline" application (PART 2).

The application process and review procedures for candidate investigators and sponsors who apply to the investigator-led call of the KCE Trials Programme are set out on our website, see https://www.kce.fgov.be/en/how-are-proposals-selected.

KCE sponsor visits

By submitting a research proposal under the Trials programme, each candidate sponsor acknowledges and accepts that KCE may at any time request a third party auditor to verify the candidate sponsor's overall capacity to perform the proposed research in accordance with the terms of its research proposal. These audit assessments may involve a site visit.

Data protection

By submitting research proposals under the KCE Trials programme, each candidate sponsor acknowledges and accepts that all personal data provided by it in connection with the research proposals, including all personal data relating to any of its proposed research team members or research collaborators (for which, to the extent required, the candidate sponsor shall obtain their consent), can be processed by KCE and its employees, representatives, agents and consultants in accordance with the below. These personal data may include, but shall not be limited to, personal data such as name and address.

The purposes of this processing are for KCE:

- (i) to be able to take informed decisions and actions under the KCE Trials programme
- (ii) to notify any candidate sponsor on upcoming research projects under the Trials programme
- (iii) to use your data anonymously to perform statistics

By submitting research proposals under the Trials programme, each candidate investigators and sponsor acknowledges and accepts that personal data can be transferred to third parties which KCE relies on for the provision of certain services related to the purposes mentioned above (e.g. members of KCE Trials panel and Trials Board, external reviewers, any third parties who may be performing quality audits of candidate sponsors and/or any of its research collaborators) and to any other non-commercial funding organisations outside KCE, also outside the European Economic Area (EEA).

Subject to the data transparency principles set out above, KCE will not disclose, share or sell personal data to any other third parties, except if KCE has received the express written consent to do so or if KCE is otherwise legally authorised to do so.

KCE confirms that personal data shall be processed proportionally within the purposes set out above and shall not be retained longer than necessary for the above mentioned use.

By sending an e-mail request to trials"at"kce.fgov.be, you can obtain from KCE free of charge the written communication of your personal data and, where appropriate, the correction of any inaccurate, incomplete or irrelevant data, or exercise any other legal right concerning your personal data.

Data transparency

By submitting research proposals under the Trials programme, each candidate sponsor acknowledges and accepts that its name, the name of the key members of its research team and the name of its research collaborators may appear on KCE's website.

In addition, once a research contract is signed and funding is released to a candidate sponsor, the candidate sponsor acknowledges and agrees that the names set forth above may appear in other literature and that the content of the research contract and protocol may be shared with third parties and will be available on the KCE website.

Applications involving tissue collection and bio-banks

If funds are requested for the creation of a tissue collection or biobank, the candidate sponsor should specify why it is necessary and is different from existing collections.

PART 2: GUIDANCE FOR COMPLETING YOUR OUTLINE APPLICATION FORM

[The following headers refer to sections of the Research Outline application form]

If you are applying to the investigator-led workstream under the Trials programme, please ensure that you read the applicable selection criteria thoroughly before starting your application. If you are unsure about any item addressed, please contact the KCE team at trials”at”kce.fgov.be.

Also on the KCE Trials website, you can find some resources for investigators following this link: https://www.kce.fgov.be/en/resources-for-investigators.

General comment: Candidate sponsors should ensure that their research outline application form provides sufficient information for KCE Trials to evaluate the application against the selection criteria outlined in the call text. To facilitate international review, submissions should be in English.

1. History of application

History of application to KCE Trials and other funders

KCE Trials: If this application is a resubmission of a research proposal submitted to an earlier call, please indicate how your current research proposal differs from previously submitted outlines, if applicable. If this resubmission is within the same call, please provide a detailed reply to each individual comment of the TB in attachment.

Other funders: Where a similar proposal has been submitted to another funding organisation, please detail *to which* funding organisation it was submitted, *when* such proposal was submitted, and the *outcome* of the submission or date of expected outcome.

Research proposals that are part of an international initiative for non-commercial pragmatic trials are eligible for the investigator-led call.* Please provide sufficiently detailed information regarding the candidate-sponsor and collaborators and possible funding sources in other countries in order to allow KCE Trials to evaluate whether the proposal falls within the scope and the non-commercial set-up of the KCE Trials programme. Co-funding of the sponsor is expected if a significant proportion of patients will be recruited abroad.

*Please note that ongoing trials (recruitment started) are excluded from this call. For possible participation of Belgian centres to already ongoing international trials, please contact trials”at”kce.fgov.be.

2. Research team

KCE Trials encourages collaborations between research centres. Models where a candidate sponsor delegates some sponsor or research tasks to other centres (including monitoring the performance of multicentre trials) are possible. Any proposed collaborations with other centres should preferably already be identified and addressed by the candidate sponsor in the outline. KCE is willing to advise candidate sponsors how such collaborations can best be organized.

Sponsor Organisation

Please give details of the organisation that will act as the sponsor if the trial is funded, as well as the main contact person. If you apply for Belgian participation to an international trial, provide here the details of the international sponsor.

National coordinating centre for international trials:

If you apply for Belgian participation to an international trial, provide here the details of the centre that will act as national coordinating centre in Belgium and its main contact person. The national coordinating centre is responsible for coordinating the trial in close collaboration with the sponsor. Tasks assigned by the sponsor to the national coordinating centre may include managing the submission of the trial to the applicable bodies and translating and adapting documentation for its country.

Clinical trial unit (if applicable)

If a clinical trial unit (CTU) or equivalent at the sponsor organisation is involved in the proposed research, please provide details and main contact people.

Chief Investigator

Please give contact details of the chief investigator. Please provide a mobile telephone number where the CI can easily be reached.

Collaborators and governance

Provide as an attachment an overview of all collaborators involved in the research, including all centres and possible subcontractors and delegated tasks of each partner.

Add a list of the planned participating sites in Belgium, and if international, countries with planned number of sites and patients per country and the details of the National Coordinator including host institution and department.

Research team capacity

Please provide details of the sponsor and collaborators experience and track-record to act as a sponsor of multicentre randomized trials (e.g. number of such trials started, completed, published).

The team (sponsor and collaborators) should be multidisciplinary and include relevant expertise in, amongst others, the clinical area concerned, in health economics, statistics, data management and in all aspects of trial management.

The Trials programme encourages the sponsor to work with, and delegate some sponsor responsibilities to, other centres where this results in a stronger submission.

Conflicts or potential conflicts of interest

Please declare any conflicts or potential conflicts of interest that the sponsor, its study team members and, where applicable, its collaborators may have in undertaking this research, including any relevant, non-personal and commercial interest that could be perceived as a conflict of interest. Please be sufficiently specific, e.g. names of companies are to be mentioned.

3. Summary of the research proposal

Pragmatic trials

KCE Trials encourages candidate sponsors to use trial interventions that reflect Belgian current clinical practice as closely as possible (i.e. pragmatic trial). The UK report[1] on risk adaptive approaches to the management of clinical trials of investigational medicinal products may provide practical ideas as to how pragmatic approaches can be implemented in studies. It complements existing waivers that exist for non-commercial trials.

Use of routine data

KCE Trials is also interested in taking advantage of the growing utility of routine data and would like investigators, where appropriate, to ask study participants to consent to long term follow-up (e.g. beyond the outcomes to be collected in the funded trial) using routinely collected data, and appropriate linkage to allow this data to be best used. This needs upfront discussion with KCE on trusted third party involvement and protection of privacy.

Research title

The project title should clearly and concisely state the proposed research in a structured way. Please spell out any abbreviations.

Example:

Outcome X after intervention A versus B: a randomized, multicentre, parallel group pragmatic trial in Y patients with disease Z.

Short title

The short title will be used in administrative documents.

Rationale for research

- What is the problem being addressed? Why is this research important in terms of improving the health of the public and/or to patients and the Belgian Healthcare system? Provide as much information as possible that is relevant to the Belgian healthcare system: a description of current practice and variation in practice, current reimbursement situation, number of patients etc.
- How does the research proposal falls within the scope of the KCE Trials programme, with special attention for the selection criteria of the 2018 call and potential return on investment? Please note that research outlines that contain insufficient information to judge the potential return on investment will receive a low score in the evaluation procedure.
- How does the existing literature support this proposal? What would the proposed study add to the existing body of evidence and ongoing trials? Applicants are invited to add in annex the search performed to find the completed as well as the ongoing trials.

Key references

A maximum of 10 key references can be added in the form. Other references can be added in attachment.

[1] http://webarchive.nationalarchives.gov.uk/20141205150130/http:/www.mhra.gov.uk/home/groups/l-ctu/documents/websiteresources/con111784.pdf

Patient and public involvement

The KCE Trials programme strongly recommends to have patients and public actively involved in the design of the study. Please briefly describe how patient and public involvement has informed and/or influenced the development of the application and how they will contribute during the lifecycle of the project (*250 words max*). This can include, for example, involvement in the choice of the research topic, choice of the outcomes, assisting in the design, advising on the feasibility of the research project etc.

Further information and resources can be found on, amongst others, the following websites:

- http://www.invo.org.uk/.
- https://www.eupati.eu/

Websites of Belgian patient federations: http://www.luss.be/ and http://www.vlaamspatientenplatform.be/

Please note that this section does not refer to the recruitment of patients or members of the public as participants in the research.

PICO

What is the research question? You should include a clear explanation of the main (single) research question phrased in PICO terms. Please be concise when completing the table. A well-defined PICO research question is a prerequisite to have a valid outline submission.

Population: target population i.e. real patients; provide main eligibility criteria
Intervention: A technology that is or could be used now in Belgium; also indicate the health service setting(s) in which the study will occur
Comparator: Usually next best treatment or usual care, but could be placebo
Outcome: Patient centred, leading to effectiveness and cost-effectiveness

Where established Core Outcomes exist they should be included amongst the list of outcomes unless there is good reason to do otherwise. Please see The COMET Initiative website at www.comet-initiative.org and www.ichom.org to identify whether Core Outcomes have been established.

Design

Design: Give a brief statement on the study design, visit schedules, outcomes and follow-up. Explain how random treatment allocation and allocation concealment will be assured. If a non-randomized design is chosen, please explain.

If the design includes an (internal) pilot or feasibility study, criteria to proceed or not to a large scale trial should be specified in advance. Please read the following information on pilot and feasibility studies carefully:
https://onlinelibrary.wiley.com/doi/epdf/10.1111/j..2002.384.doc.x

http://www.consort-statement.org/extensions/overview/pilotandfeasibility

Visit schedule: specify which visits are standard treatment and which additional/study specific. Please add a flowchart and/or visit schedule in attachment.

Outcomes: describe the way and time points that outcomes will be measured (PRO, questionnaires, EQ-5D etc.…). Details should include justification of the choice of outcome measures where a legitimate choice exists between alternatives. If the study includes a health economic component, state from what perspective costs and benefits will be considered, and (briefly) how these will be collected.

Follow-up: discuss and specify any long term follow-up plans after the main analysis. Sufficiently long follow-up should be included to define long-term benefit and risks for patients and the Belgian health care system.

KCE Trials encourages candidate sponsors to use trial interventions that reflect Belgian current clinical practice as close as possible (i.e. pragmatic trial). For information on pragmatic trials, please visit our "resources for investigators" website: https://www.kce.fgov.be/en/resources-for-investigators.

The UK report on risk adaptive approaches to the management of clinical trials of investigational medicinal products may provide practical ideas as to how pragmatic approaches can be implemented in studies. It complements existing waivers that exist for non-commercial trials. MRC/DH/MHRA Joint Project - Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products

Protocol

A key element of the FRP is the protocol which should be provided as a separate document. It should contain the elements detailed in ICH good clinical practice (see section 6 of E6 guidelines[2]). To facilitate the writing of the protocol by the candidate sponsor and the review process, we strongly encourage the use of the protocol template provided, which has been developed in UK by NHS Health Research Authority[3] and has been adapted to the Belgian context by KCE Trials.

Using the template: when a section is not applicable in the specific setting, please leave the section title and indicate 'not applicable' (so that the numbering of sections stays the same). If the candidate sponsor prefers to use their own template, then they must provide a table of correspondence between sections in the protocol used and the template provided, and should provide the same level of detail as requested.

This is the advised structure for the protocol (see template)

GENERAL INFORMATION
TITLE PAGE
RESEARCH REFERENCE NUMBERS
SIGNATURE PAGE
TRIAL SUMMARY
FUNDING
KEY TRIAL CONTACTS
ROLE OF SPONSOR AND FUNDER
ROLES & RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITTEES, GROUPS AND INDIVIDUALS
LIST of CONTENTS
LIST OF ABBREVIATIONS
TRIAL FLOW CHART
SECTION
1. BACKGROUND
2. RATIONALE
3. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS
4. TRIAL DESIGN
5. STUDY SETTING
6. ELIGIBILITY CRITERIA
7. TRIAL PROCEDURES
8. TRIAL MEDICATION
9. PHARMACOVIGILANCE
10. STATISTICS AND DATA ANALYSIS

[2] http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html

[3] http://webarchive.nationalarchives.gov.uk/20141205150130/http:/www.mhra.gov.uk/home/groups/l-ctu/documents/websiteresources/con111784.pdf

[3] http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html

[3] http://www.hra.nhs.uk/about-the-hra/consultations-calls/closed-consultations/protocol-guidance-template-use-clinical-trial-investigational-medicinal-product-ctimp-consultation-use/

11. DATA HANDLING
12. MONITORING, AUDIT & INSPECTION
13. ETHICAL AND TRIAL ADMINISTRATION
14. DISSEMINATION POLICY
15. REFERENCES
16. APPENDICES The appendices should contain: 1. An evaluation of the classification of the study (based on the new Directive) as low risk interventional or not and the justification for the classification 2. The details of study management / responsibilities (including data management plan) 3. The signed authorisation of participating sites 4. A schedule of procedures, with an indication of whether the tests/ visits/ interventions are standard practice or not 5. A safety reporting flowchart 6. A protocol amendment history

Lay summary

Provide a plain language summary in English that can be easily understood by non-professionals, such as representatives of patients and the public. The lay summary of funded trials will be translated in Dutch and French and published on the KCE Trials website.

Sample size

Please provide here the planned sample size of the study (absolute number only).

Statistical justification for sample size

Provide sufficient details of the sample size calculation so it can be reproduced (superiority vs non-inferiority, alpha, beta, clinically relevant difference). Detail the population(s) for the analyses planned (intention to treat, per protocol, safety), primary analysis (define the time point, variable, test that will be used, details of any adjustments), secondary analyses.

You may find useful information in the following guidance from the NHS Health Research Authority: http://www.hra.nhs.uk/documents/2014/05/guidance-questions-considerations-clinical-trials.pdf

Health economic considerations

Describe health economic considerations by stipulating the expected impact (if any) on mortality, quality of life and cost items. For cost items, please include at least current costs for all interventions, both for RIZIV-INAMI and patients. Also consider the impact on adverse events and related costs (e.g. hospitalisations) and describe the possible impact on other important variables. The focus should be on items that are different (i.e. incremental elements) between the alternative treatment arms in the trial, both in the short and long term. Think for example about possible differences in follow-up, productivity, etc. As such, you can generate the hypothesis whether the results of the research could lead to net saving for the Belgian healthcare system budget or to the introduction of more cost-effective interventions.

To be able to have an idea of the possible budget impact, please also provide an estimate of e.g. yearly number of patients in Belgium and/or frequency of use.

An option to consider, if of interest for the design of the pragmatic trial or economic analysis, could be the use by the candidate sponsor of study subjects' Belgian national number (rijksregisternummer/ numéro national) to acquire data, for examples RIZIV-INAMI billing data. This needs upfront discussion with KCE Trials on trusted third party involvement and protection of privacy.

Protocols of clinical studies funded under the KCE Trials programme have been designed with a later possible economic analysis in mind. For example, to facilitate a later cost-utility analysis, quality of life data are collected during the trial (EQ5D). In some trials, after patient informed consent, the national number of the patient will be collected by the trusted third party to allow for a data coupling with healthcare consumption data (billing data).

- As any further data analyses, an economic analysis can of course be conducted by the sponsor of the trial and the chief investigator, totally independent from KCE. The budget for such analysis is not part of the trial budget covered by KCE.
- In addition, an economic analysis can be part of a KCE health technology assessment (HTA) project. HTA projects are conducted by KCE at its own costs as part of its annual work programme approved by the KCE board, and following the KCE processes. The decision for KCE to perform a HTA on the topic will depend on the trial results and the prioritisation of the topic among the topics introduced that year. Each KCE HTA project includes a literature review. Data from different studies may be included. A meta-analysis may be conducted for that purpose, including the results or the coded individual data of the funded trial. HTA projects are conducted internally at KCE or are outsourced to a certain extent using a public tender procedure. In any case, KCE uses external experts during the project. For an HTA following a trial funded by KCE Trials, KCE would among others, invite the team of the chief investigator to act as external clinical experts to accompany the HTA project. In case there is a substantial contribution and in accordance with academic standards external experts that accompany a KCE project will be requested to be a co-author of the KCE report and a possible scientific publication based on the KCE report.

Reply to the comments from the Trials Board

(only to be completed if this proposal has been submitted to KCE Trials before)

Please enter your reply to the comments by the Trials Board (mentioned in the decision letter), and how it affects your revised submission.

Changes in the project since previous submission

(only to be completed if this proposal has been submitted to KCE Trials before)

Any other significant changes in the research proposal (e.g. design, objectives, budget) since the last submission have to be mentioned and explained in this section.

Unless agreed otherwise by KCE, a previously rejected application cannot be resubmitted to the Trials programme within one year of the original decision letter. For researcher-led workstreams (not applicable for the 2016 programme), resubmissions will only be accepted if applicants can demonstrate that their research proposal has been changed significantly and is essentially a new proposal.

4. Timelines and feasibility

Timetable

Provide an overview of the timelines of your research proposal if your research proposal would be recommended for funding by the Trials Board. Consider the Trials Board decision as month zero and indicate the estimated timelines in months after the TB decision for each listed event.

Please be realistic about your possible start date *inter alia* taking into account the necessary time to enter into the applicable research contract, and any approvals by governmental bodies and/or ethics committees that you may need prior to starting your project. Please take into account that the necessary capacity in term of manpower to assure continuity needs to be in place.

If you are submitting a Full Research proposal (FRP): please provide a concise summary of the project plan of investigation, preferably in the form of a monthly project timetable showing the scheduling of all key stages in the project, their expected duration, and the timing of key milestones throughout the project including the production of outputs as attachment. Add details of how the project will be managed.

Recruitment considerations

Please provide information on the planned recruitment rate (a calendar with the estimated number of patients per month from the start to the end of recruitment). Provide evidence that the number of participating sites is sufficiently high and that the investigators have access to a sufficient number of eligible patients to keep the planned recruitment period as short as possible, while fully respecting the scientific rigour of the trial. Provide details of the number of patients seen in each of the participating sites last year and what percentage may be eligible for the proposed research.

Add details of any potentially competing trials (current and in the near future).

5. Research costs

Total research costs

Pride here the total amount of funding that is requested to KCE Trials, excluding possible funding received from other sources (absolute number only).

The initial research outline requires a 'financial estimate' of the research costs. Successful outlines will be invited to submit FRP's including development of full study cost assessments with financial approvals. All costs need to be fully justified by the candidate sponsors to demonstrate that the study offers good value for money for the Belgian healthcare system and tax payer.

Please enter estimated values for the research costs and add the current reimbursement practice for any investigations under study.

The Trials programme accepts that some variance in costs is likely to occur between outline and FRP and will carefully scrutinise all full application costs and any variance from the outline.

Research costs include (amongst others and as applicable): protocol development including statistics, database design, set-up and data management, management of contracts and finances, regulatory submissions, site selection, training and management, quality assurance and monitoring, pharmacovigilance, drug and sample management, analysis and reporting. All planned analyses should be justified. Data that will not be analysed should not be collected.

A breakdown and justification of the budget should be provided as an attachment using the excel budget template provided with the call. Guidance notes to complete the budget tool are available on the website. For international trials, please use the specific budget tool and guidance notes.

Costs for the trial interventions (medication, devices, other) are part of the research costs unless the approval is obtained to use the RIZIV-INAMI (or any of its counterparts) reimbursement for the interventions.

Funding or support from other sources

In case you will receive funding or support from any other source in relation to this proposal, e.g. funding for lab research or biomarker development linked to the study, provision of medication or placebo, provide sufficient details about the type and extent of support.

Note: co-funding is not allowed, unless explicitly agreed otherwise by KCE Trials. All research partners providing funding or other types of support should accept the terms and conditions of the KCE Trials programme.

6. Terms and conditions

Proposed terms of the research agreement

Following the selection and approval of an FRP, KCE and the selected candidate sponsor will enter into a research agreement prior to the initiation of the study. A template research agreement has been drafted by KCE in consultation with representatives from the Belgian university hospitals. KCE expects that candidate sponsors by signing the sponsor support letter accept the terms and conditions included in this template KCE-sponsor research agreement.

Any major remarks on the terms and conditions should be discussed with the KCE Trials team before submitting a proposal for funding. In that case only and after discussion with KCE Trials, please attach a copy of the template research agreement with your main comments/reservations in respect of the proposed terms of the template research agreement highlighted.

Possible commercialisation

Trials funded within the framework of the KCE Trials programme should have a primary aim that is non-commercial. However, in some cases results of the trial may lead to commercialisation of for example software programs, apps or biomarker tests. Please indicate here which commercialisation could possibly result from the trial.

General comments

Use this box to add any information you would like to provide to KCE Trials and the Trials Board.

Attachments

Please upload the following documents on the submission portal for applicants (in PDF format):

1) This application form
2) Signed and dated short English CV of chief investigator (max 1 page)
3) A signed support letter from the candidate sponsor or, if international sponsor, a signed support letter from the candidate Belgian coordinating centre
4) A signed commitment letter from the international sponsor
5) A description/overview of the governance of the trial, including information on all partners/sites and delegated tasks and a list of participating sites
6) A one page flowchart and/or visit schedule
7) Description of the literature search performed to find completed as well as ongoing trials with any additional references
8) A breakdown and justification of the requested budget with individual/role performing the task (in the excel template provided, do not convert to PDF)
9) In case this was discussed with KCE Trials before submission, the template research agreement (see KCE website) with comments in tracked changes.
10) Draft protocol if submitting a full research proposal (second stage)
11) If this the proposal has been submitted before, please attach an overview with responses to the TB comments.

Please mark in the table in the application form which attachments are added to the application and name the files as advised.

KCE TRIALS PROGRAMME

ANNEX 1 - ASSESSMENT CRITERIA

Need for Evidence	• The importance or burden of the health or care problem to those who would use the evidence generated by the proposed study. In particular, whether the trial would likely lead to improved health and care in Belgium and contribute to change in practice. • What the proposed study would add to the existing body of knowledge based on a well-documented search for completed and ongoing research.
Potential return on investment (ROI) for the Belgian health care system	• Highest score: substantial cost savings are expected. Either substantial savings per patient for small populations as well as savings for large populations that are substantial because of the size of the population fall within this category. Interventions with an equivalent effectiveness that result in relevant cost savings compared with existing alternatives also fall within this category. • High score: Increased patient benefit comes at acceptable extra expense for society. • Low score: It is very questionable whether the increased patient benefit comes at an acceptable extra expense for society. Research outlines that contain insufficient information to judge the expected ROI will receive a low score.
PICO	• The trial is a comparative effectiveness trial, comparing two interventions (including no treatment) that are already in use in Belgium in a given indication, without limitation in terms of therapeutic domain or type of intervention or comparator. Medication used off-label in daily practice is considered in scope. If the trial is a repurposing trials, the following conditions are met: ○ The drug is off patent. ○ There is a potential of high return on investment. ○ There is substantial underlying evidence that supports moving to a large-scale confirmatory randomized trial. • The trial intervention(s) should reflect current clinical practice as close as possible. • Outcomes are patient centred and include the core outcome set, if available.
Design	• The study design would answer the research question proposed. • A pragmatic design is to be selected if this would be most informative. • Trial design should allow for sufficiently long follow-up. • A randomised, multicentre design is highly preferred. • The use of centralised randomisation and e-CRFs are recommended. • Only a limited set of variables, needed for the pre-planned analyses, are to be collected. All variables collected need to be well justified.
Value for Money	• The proposed costs of the research are reasonable and commensurate with the work involved. • The costs of the trial are reasonable in relation to the likely benefit of the research to decision-makers, patients and the public. • The trial results can have an immediate and important impact on the efficiency (decrease of the costs and/or improvement of the results) of the Belgian healthcare system, preferably without the need for an additional implementation project (see return on investment).
Patient and public involvement	• KCE strongly encourages patient involvement in research. The involvement of patients and/or public in the development of the project (selection of patient-relevant study endpoints, feasibility of trial assessments) and their continued involvement through the lifecycle of the research project is required for submissions to the Call. • A lay summary of the study in English should be included.

Sponsor	• The sponsor qualifies as non-commercial sponsor under the applicable laws, including the law of May 7, 2004 or equivalent e.g. if the sponsor is not located in Belgium. • The sponsor's team has the necessary skills, procedures and experience in conducting non-commercial multicentre trials and has the ability to comply with all sponsor related obligations under the applicable laws, including the law of May 7, 2004. The candidate sponsor allows KCE to verify these requirements during a visit. • The investigators in all study sites demonstrate an expertise in the disease and patient population that will be studied. • The holder of the patent of a medicinal product or of a registered trademark of a medical device to which the experiments relate is neither directly nor indirectly the sponsor of the experiment. • The sponsor exercises the intellectual property rights to the concept of an experiment, its implementation and the scientific data resulting from it. • The agreement should be in line with the European state aid rules and regulations.
Timelines and feasibility	• The number of participating sites is sufficiently high and the investigators have access to a sufficient number of eligible patients such that the planned recruitment period is kept as short as possible while fully respecting the scientific rigour of the trial. In addition, measures are in place to maximally reduce the risk of a delay in recruitment including the absence of competing trials that may hamper patient recruitment. The investigators allow KCE to verify these requirements during a study site visit. • The risk of recruitment delay is considered low. • The relevance of the trial results at the time of publication should be justified.
Implementation	• The trial results can have an immediate and important impact on the efficiency of the Belgian healthcare system, preferably without the need for an additional implementation project.
Terms and conditions of the research agreement	• The terms and conditions of the proposed collaboration between sponsor and KCE should be accepted by the sponsor.
Need for Evidence	• The importance or burden of the health or care problem to those who would use the evidence generated by the proposed study. In particular, whether the trial would likely lead to improved health and care in Belgium and contribute to change in practice. • What the proposed study would add to the existing body of knowledge based on a well-documented search for completed and ongoing research.

Potential return on investment (ROI) for the Belgian health care system	• Highest score: substantial cost savings are expected. Either substantial savings per patient for small populations as well as savings for large populations that are substantial because of the size of the population fall within this category. Interventions with an equivalent effectiveness that result in relevant cost savings compared with existing alternatives also fall within this category. • High score: Increased patient benefit comes at acceptable extra expense for society. • Low score: It is very questionable whether the increased patient benefit comes at an acceptable extra expense for society. Research outlines that contain insufficient information to judge the expected ROI will receive a low score.
PICO	• The trial is a comparative effectiveness trial, comparing two interventions (including no treatment) that are already in use in Belgium in a given indication, without limitation in terms of therapeutic domain or type of intervention or comparator. Medication used off-label in daily practice is considered in scope. If the trial is a repurposing trials, the following conditions are met: o The drug is off patent. o There is a potential of high return on investment. o There is substantial underlying evidence that supports moving to a large-scale confirmatory randomized trial. • The trial intervention(s) should reflect current clinical practice as close as possible. • Outcomes are patient centred and include the core outcome set, if available.
Design	• The study design would answer the research question proposed. • A pragmatic design is to be selected if this would be most informative. • Trial design should allow for sufficiently long follow-up. • A randomised, multicentre design is highly preferred. • The use of centralised randomisation and e-CRFs are recommended. • Only a limited set of variables, needed for the pre-planned analyses, are to be collected. All variables collected need to be well justified.
Value for Money	• The proposed costs of the research are reasonable and commensurate with the work involved. • The costs of the trial are reasonable in relation to the likely benefit of the research to decision-makers, patients and the public. • The trial results can have an immediate and important impact on the efficiency (decrease of the costs and/or improvement of the results) of the Belgian healthcare system, preferably without the need for an additional implementation project.
Patient and public involvement	• KCE strongly encourages patient involvement in research. The involvement of patients and/or public in the development of the project (selection of patient-relevant study endpoints, feasibility of trial assessments) and their continued involvement through the lifecycle of the research project is required for submissions to the Call. • A lay summary in English, Dutch and French should be included.
Sponsor	• The sponsor's team has the necessary skills, procedures and experience in conducting non-commercial multicentre trials and has the ability to comply with all sponsor related obligations under the applicable laws, including the law of May 7, 2004. The candidate sponsor allows KCE to verify these requirements during a visit. • The investigators in all study sites demonstrate an expertise in the disease and patient population that will be studied. • The candidate sponsor should qualify as non-commercial sponsor under the applicable laws, including the law of May 7, 2004 or equivalent e.g. if the sponsor is not located in Belgium.

	• The holder of the patent of a medicinal product or of a registered trademark of a medical device to which the experiments relate is neither directly nor indirectly the sponsor of the experiment. • The sponsor exercises the intellectual property rights to the concept of an experiment, its implementation and the scientific data resulting from it. • The agreement should be in line with the European state aid rules and regulations.
Patients	• The number of participating sites is sufficiently high and the investigators have access to a sufficient number of eligible patients such that the planned recruitment period is kept as short as possible while fully respecting the scientific rigour of the trial. In addition, measures are in place to maximally reduce the risk of a delay in recruitment including the absence of competing trials that may hamper patient recruitment. The investigators allow KCE to verify these requirements during a study site visit.
Timelines	• The risk of recruitment delay is considered low. • The relevance of the trial results at the time of publication should be justified.
Implementation	• The trial results can have an immediate and important impact on the efficiency of the Belgian healthcare system, preferably without the need for an additional implementation project.
Terms and conditions of the research agreement	• The terms and conditions of the proposed collaboration between sponsor and KCE should be accepted by the sponsor (see collaboration agreement version 1.2).

In case of a resubmission, KCE will include the reply of the candidate sponsor to the TB recommendations as an additional criterion in the assessment.