

KCE TRIALS PROGRAMME

KCE Trials 2024 Investigator-led call

Deadline for submission: 24th September 2024 13h

Call text

21 May 2024	Call opens on KCE Trials research management platform (https://kce.smartsimple.ie/)
7 June 2024; 10h	Information session on scope and Q&A
24 September 2024; 13h	Deadline for submission of Research Outline (call closes on KCE Trials research management platform)
21 November 2024	Decision on prioritisation of proposal (by Prioritisation Group)

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1. BACKGROUND

Many questions in healthcare are currently not sufficiently studied in clinical trials, despite their high societal importance (e.g. comparing medicines which are commonly used but which haven't been directly compared, comparing lifestyle changes to a medical intervention, comparing surgery to physiotherapy for specific indications or questions addressing the needs of older people). **'Comparative effectiveness' studies compare two treatment options (with 'no treatment' being one of the possible treatment options) that are already used in clinical practice for a given indication, but have not yet been sufficiently directly compared (i.e. which of the two treatment options works best in daily practice and is the most cost-effective).** Since 2015, KCE manages a national funding programme of such pragmatic practice-oriented clinical trials, the KCE Trials Programme. To date, over 50 clinical trials have been selected within this programme (see [funded trials](#) for more information or [our dynamic dashboards](#) for recruitment progress).

The 2024 investigator-led call is the 9th national call for comparative effectiveness proposals (see [calls](#) for more information on past and present calls). The submitted trials should contribute to better patient care, should show clear value for money and should have the potential for return on investment. Accepted study interventions for treatment or prevention are not limited to drugs or medical devices but also include a broad range of healthcare interventions, for example psychotherapy, physiotherapy, diets, diagnostic tests or surgery. In addition, repurposing trials using off-patent drugs are eligible for funding under certain conditions. The budget available for this call amounts to € 9.0 million.

2. CRITERIA

2.1 Who can submit to the 2024 investigator-led call?

This call is investigator-led, meaning that investigators submit their own research idea as a study proposal outline and should have the support of a non-commercial sponsor to perform the trial themselves. It is strongly recommended that trials are developed and conducted with the support of a clinical trial centre or equivalent. Only multicentre studies are eligible, with participating centres including at least one recruiting centre from each region (Flanders, Brussels, Wallonia), unless there is a good justification not to do so. Also, trials run in the first-line setting, for example in general practice, should have good representation from participating investigators in all three regions.

The participation of Belgian centres to an international non-commercial trial within the scope of this call, is also eligible for funding.

The aim of the study cannot be commercial, and the sponsor should be a non-commercial sponsor, in Belgium or abroad. In the latter case, KCE Trials will provide funding for the participation of Belgian centres through a Belgian coordinating centre (BCC).

A letter of support, using the template provided by KCE Trials, signed by the candidate sponsor confirming acceptance of the trial sponsor obligations and acceptance of the terms and conditions included in the template KCE-sponsor research agreement should be included in the submission. The Belgian candidate sponsor or the BCC should be a non-profit organisation that can function as sponsor of non-commercial multicentre trials and has the ability to comply with all sponsor related obligations. If the sponsor is located abroad, a signed commitment letter by the international sponsor confirming acceptance of the KCE Trials terms and conditions regarding the non-commercial nature of the trial and data sharing conditions (see below) and a signed letter of support by the BCC should be included, both using the KCE Trials templates.

If funding is requested for participants recruited abroad, justification should be provided and will need to be approved. In general, for trials with a Belgian sponsor and participants recruited abroad, participation of other funders, to cover site costs for participants recruited abroad and to contribute to the sponsor costs, will be required.

2.2 Scope

Inclusion criteria

The primary aim of the study is non-commercial, this means:

- The candidate sponsor (and the Belgian Coordinating Centre "BCC", if applicable) should be a non-profit organisation that can function as sponsor of non-commercial multicentre trials and has the ability to comply with all sponsor related obligations.

- The holder of the intellectual property rights on the studied intervention or comparator to which the trial relates is neither directly nor indirectly the sponsor/BCC of the trial.
- The sponsor exercises the intellectual property rights to the concept of the trial, its implementation and the scientific data resulting from it.
- If there is a commercial interest in the study (e.g. the study requires the use of drugs, apps or medical devices), an exclusivity criterion comes into play. In general, the results of the study cannot bring a potential benefit to a single company only¹.
- Studies on the effect of medical devices, tools (including software and apps) or on-patent drugs are only in scope, provided that there is a strong justification why the study would not be performed by the marketing authorisation holder or manufacturer. In this situation an expected high return on investment is required.
- The funding granted under the research agreement complies with the European state aid regulations.
- The sponsor, chief investigator and research team should have no conflict of interest in regards with the performance and possible results of the trial.

Design

- The trial is randomised (at individual level or in clusters) and multicentric (with at least one recruiting centre in each region, unless there is a good justification not to do so).

Comparative effectiveness studies

- The trial is a comparative effectiveness trial, comparing two therapeutic or diagnostic interventions (no treatment/no test can also be an option) that are already in use in daily practice in Belgium in the studied indication.
- Medication used off-label in daily practice is considered in scope.
- Studying an intervention that is already in use in a patient group, (e.g. adults), in another patient group, (e.g.; children, elderly, oldest old) can be considered in scope. A change of timing, e.g. first line versus second line, or change in dosing or duration of the treatment can also be considered in scope.

Drug repurposing studies

- Repurposing of a drug(s) for an indication for which it is currently not used in daily practice may be in scope if the following 4 conditions are met:
 - The drug is off-patent and there is no secondary patent limiting the freedom to operate or implementation of the study.
 - The available evidence suggests that there is a potential for high return on investment (see Annex I).
 - There is substantial underlying peer-reviewed evidence that supports moving to a large-scale confirmatory randomised trial.
 - The drug is authorised and commercialised in Belgium (or in use in daily practice in Belgium).

Exclusion criteria

Started studies

- Studies for which recruitment has already started in Belgium, or which have already been submitted to a Belgian ethics committee and/or to the FAMHP (Federal Agency for Medicines and Health products) are out of scope. International studies that have already started abroad (but not in Belgium) are eligible if all other criteria are met.

Implementation studies and quality improvement studies

- If the primary aim of the studied intervention is to promote the uptake of research findings, the study is considered implementation research, which is out of scope. Interventions that aim to improve

¹ For instance, studies including drugs that are available in generic form or studies in medical devices that are produced by several companies would be considered as having an aim which will not bring commercial benefit to exclusively one company. Studies aiming to extend the indication of drugs still on patents or studies using unique medical devices would be considered as having a commercial aim (and should therefore be funded by the company itself).

implementation of existing guidelines, health policies, programmes and practices are also out of scope, as are studies that aim to improve quality of care.

Development and innovation studies

- Drugs without marketing authorisation in Belgium are out of scope except if already widely used in Belgium. Medical devices without a CE label are out of scope.
- All types of interventions, including interventions related to organisation of care, should already be in use in practice, outside of the framework of research or development. Interventions that have been used only within the framework of clinical research or pilot testing are out of scope.
- Proof of concept studies are out of scope. There should be substantial underlying peer-reviewed evidence that supports moving to a large-scale confirmatory randomised trial.

Mobile health studies (apps)

- Software and apps used as part of the intervention that are not fully developed, piloted and that do not meet all regulatory requirements on data protection are out of scope. Apps that are not used in daily practice in Belgium are also out of scope.
- Study proposals on software and apps should also include an implementation plan which is in agreement with the non-commercial aim of the KCE Trials programme. Proposals without this implementation plan will be considered out of scope.

2.3 Budget and duration of proposed trial

The duration of the study should be realistic and be able to generate results preferably within five years. A long term follow-up study after collection of the primary outcome can be included if appropriate.

The proposed budget of the trial must be reasonable and commensurate with the work involved. A thorough evaluation of the proposed budget is part of the assessment procedure. A budget tool and guidance is used to calculate the trial budget (see below). By submitting an application, the candidate sponsor agrees to the principles of the budget tool and guidance notes. Although in principle no maximum amount is defined, the budget granted to one trial can never exceed half of the total available call budget. The final budget will be negotiated and approved by the KCE Trials team and should not differ by more than 10% from the initially submitted budget.

2.4 Patient and public involvement

KCE strongly encourages patient involvement in research. The involvement of patients and/or the public in the development of the project (e.g. the choice of the research question, the 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. Therefore, KCE Trials prepared a patient involvement document to be completed and added to the application (see links and downloads).

2.5 Selection and prioritisation criteria

Proposals that are valid and in scope will be evaluated by the Panel and Trials Board (see “4. Selection procedure”). The detailed evaluation criteria for the 2024 call are listed in Annex I.

Proposals will be evaluated based on the information available in the submission. Applicants should make sure that sufficient clear information is available in their proposal to evaluate the submission according to the listed criteria.

Prioritisation criteria

Study proposals will be prioritised based on:

- The need for generating new evidence in clinical practice is large.
- There is a possible efficiency improvement for the Belgian health care system.
- There is underlying peer-reviewed evidence that supports moving to a large-scale confirmatory randomised trial.

In addition, the following criteria will be taken into account during the prioritisation process:

- The number of people potentially impacted by the intervention is large.

- The expected effect of the intervention/improvement is large (mandatory if the previous criterion is not met).
- Funding of the study by commercial stakeholders is unlikely and/or not warranted.
- The geographical spread of the participating centres is well balanced over the different regions.
- The research question has been put forward as a priority by patient groups or is ranked high on a research agenda developed in collaboration with patients.
- The overall portfolio of the KCE Trials programme remains well balanced in terms of disease areas, types of interventions and settings.
- The study budget is acceptable within the overall budget of KCE Trials.
- Value for money: the trial leads to increased efficiency of the health care system in addition to benefit for patients in one of the following ways:
 - If positive, the trial may lead to savings for healthcare payers based on the trial results; while patient benefit remains at least the same.
 - Occasionally, a trial may deliver immediate savings for health care payers, just by running the trial, in addition to possible patient benefit. Examples are trials that investigate a shorter duration of an expensive drug/treatment or trials that compare an expensive to a cheaper treatment option, both of which are currently reimbursed.
 - Based on the trial results, there is a possibility to increase patient benefit/quality of life at a reasonable cost.
- As older people generally are underrepresented in clinical trials and we have observed that studies in older people are currently underrepresented in the KCE Trials portfolio, we would welcome proposals studying older people. However, this should not be considered a limitation of the accepted study populations or the scope of the call.

3. How to submit

- The call will be open to submissions from 21st May 2024 until 13h on 24th September 2024.
- As a first step, candidates are asked to submit a research outline. Shortlisted candidates will be invited to submit a full research proposal (FRP) (with the study protocol) in a second step.
- We suggest to contact KCE Trials (trials"at"kce.fgov.be) in advance if you want to resubmit a proposal that was not funded in a previous call.
- All submissions must be done using the KCE Trials [online submission platform](#). To be able to submit, you have to create an account, if you do not already have one. Please create an account as soon as possible and at least 1 week before the submission deadline to enable us to correct possible problems with the online submission platform. Once you have created the account, you can find information to start your submission under the "funding opportunities" tab.
- You may prefer to prepare your application using the application form in Word format, which is available on the [KCE Trials website](#) for your convenience (no application submitted in the word template will be accepted). This document also contains guidance on how to complete your application.
- Only the chief investigator can start an application and complete the submission. However, other members of the research team can help completing the application form if added to the contacts list. **You are encouraged to contact your statistician, legal advisor, health economist, clinical trial centre or equivalent early in the process and give them access to your application** to complete their parts.
- A detailed budget should be submitted using the dedicated budget tool, **for which separate guidance notes are available**. It is advisable to complete the budget tool in collaboration with the clinical trial centre.
- All documents for the submission are detailed below in section "6. Links & downloads" and can be found on our [website](#).
- To be deemed valid and to enter the selection process, a submission must:
 - Be written in English.
 - Be submitted through the [online submission platform](#) (kce.smartsimple.ie) before the deadline.
 - Include details of the chief investigator and candidate sponsor.
 - Include a sponsor support letter using the KCE Trials template or, for international trials with a non-Belgian sponsor, a support letter from the Belgian coordinating centre and a

commitment letter signed by the international sponsor, using the applicable KCE Trials templates. The letter of support needs to be signed by the legal representative of the sponsor (usually the CEO), or an official delegate.

- If there is any collaboration with a commercial partner (e.g. delivery of free/discounted medication, apps, medical devices etc.), a signed commitment letter from the commercial partner accepting the KCE Trials terms and conditions using the applicable KCE template should be included in the initial submission. This will be used in order to assess the non-commercial nature of the trial and additional information may be requested. Standard purchasing under normal market conditions does not require a signed commitment letter.

4. Selection procedure

The evaluation and selection of research proposals for trials with Belgian sponsors comprises several steps:

1. All valid research outlines received will be assessed for whether or not they are within the scope of the 2024 call as defined in this call text by the KCE Trials Prioritisation Group (PG).
2. A maximum of 15 proposals will be discussed by the Panel. If more in scope research outlines are received, the research outlines with a low score on prioritisation criteria may be excluded at this stage by the PG.
3. Research outlines that are within scope will be scored by a Panel of clinical experts, health economists and representatives of patients for their relevance and importance for the Belgian health care system.
4. Based on the Panel's scores, the PG will prioritise the most relevant research proposals for further evaluation. A maximum of 10 proposals will be forwarded to the Trials Board (TB).
5. Candidates will be informed about the results of the first steps of the selection procedure in December 2024.
6. Shortlisted research outlines that are considered highest priority will be evaluated for their methodological quality and scientific value by the TB (see Annex I). The first TB meeting for the 2024 call will be planned at the end of 2024.
7. For outlines that are shortlisted to continue to the full research proposal (FRP) stage (or for resubmission of a research outline) during the first TB meeting, the sponsor team will have at least six weeks to develop and submit their FRP (including a draft study protocol).
8. The evaluation of your proposal by the TB may involve several review cycles. Proposals submitted to the 2024 investigator-led call can be recommended for funding by the TB in March 2025 at the earliest. A proposal will be reviewed by the TB a maximum of five times.
9. For this call and based on the current yearly budget, KCE Trials aims to fund 4-6 studies (depending on the size, complexity and quality of proposals received).

International trials with a Belgian sponsor with the majority of patients recruited in Belgium follow the procedure as described above.

For international trials with only a minority of patients recruited in Belgium, the review of research outlines will be included in the review by the KCE Trials panel and prioritisation by the PG as other proposals. If selected, the research outlines will not be forwarded to the TB as protocols for international trials are usually written in consensus with the international partners. The final draft protocol and budget for Belgium participation has to be submitted to the TB within the timelines of the call. Protocols for international trials will be reviewed by the TB once, in a 'take it or leave it' fashion. Exceptionally, a second review by the TB can be done, if requested changes can still be implemented by the international sponsor or additional information provided.

More information on the selection process can be found [here](#) on the KCE website. An overview of the important dates is added on the cover page of this call text.

5. Financial and legal issues

5.1 Terms and conditions

By submitting a research proposal to the 2024 investigator-led call, and as confirmed in the sponsor support letter, the candidate sponsor and research team accept the terms and conditions of the KCE Trials programme, as stipulated in the research agreement template (last version available at the publication of the call text) that can be found on the website.

In particular, applicants should carefully read the terms and conditions on ownership, data sharing and the non-commercial primary aim of the trial. Co-funding or collaboration with a commercial entity (including

provision of drug or non-standard preferential discounts) is only allowed if accepted by KCE in writing. The party offering support should accept all the principles set forth in the KCE Trials research agreement template prior to submission. If selected and funded, the contracts with parties offering support need to be reviewed and approved by KCE Trials.

If candidate research teams have major comments on the research agreement template, this should be discussed with the KCE Trials team before submitting a proposal. In that case and if a prior written agreement is given by KCE Trials, the template with these major comments in tracked changes must be attached to the submission.

If your proposal involves medicinal products or medical devices, you should consult with your legal advisors or technology transfer office (TTO) early in the process to check that your freedom-to-operate is not limited by intellectual property rights (e.g. primary or secondary patents) and that you are able to comply with the KCE terms and conditions. If you are, at a later stage, invited to submit a FRP, a report containing details of a full-scale search may be requested together with your implementation plan.

Please note that KCE shall remain entitled at all times to postpone, suspend and/or withdraw review of or support for any research proposal (even during the negotiation of the research agreement) upon its own discretion and that KCE shall under no circumstances be obliged to select any pending proposal or enter into a research agreement after FRP selection. Applicants can withdraw their proposals at any time before signature of the research agreement with KCE.

Questions and any possible complaints regarding decisions of the Trials Board, Prioritisation Group and KCE Board can be sent to trials@kce.fgov.be. Decisions are final however and there is no organised administrative appeal procedure for candidate sponsors to appeal the decisions.

5.2 Budget

The budget for the proposal should be submitted using the budget tool designed for this call. It is important for the evaluation and selection procedure that budgets are delineated in a standardised format. For Belgian trials the budget covers the sponsor costs and site costs.

For some studies a pilot or feasibility study will be requested by KCE Trials for which a separate budget will be foreseen in due course. For international trials the budget will depend on, amongst other things, the Belgian contribution to the study.

You are advised to carefully read the guidance notes related to the budget tool template or the budget tool BCC template for international trials as they contain useful information that will help you better understand the different tasks and the rationale for the formulas used when preparing the budget for your trial. You are encouraged to contact your clinical trial centre at the early stage of developing your budget.

Please note that once the budget is agreed upon (usually after FRP recommendation to fund), this will be used to develop a payment schedule. In order to stimulate timely participant recruitment and performance of the study as planned, the majority of the costs in the payment schedule will be paid on the basis of milestones (e.g. participant randomisation, trial report, etc.). Follow-up of milestones and payments will be coordinated by the KCE Trials team.

5.3 Funding for Research on Research (ROR) associated with KCE funded trials

KCE trials is willing to fund justified qualitative research (process evaluation of complex interventions) and Studies Within A Trial (SWATs²) which are embedded in KCE Trials' funded studies. A limited budget can be included.

Some studies may face inherent challenges with including a representative group of participants. Examples can be found on the [NIHR Improving inclusion of under-served groups in clinical research](https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-019-3980-5) webpage or [the INCLUDE Ethnicity Framework](https://www.qub.ac.uk/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/SWATSWARInformation/Repositories/SWATStore/) website. In this case KCE Trials welcomes research projects aimed at improving inclusion and is willing to provide a limited budget to support this and/or fund this research.

² These are self-contained research studies embedded within a host trial that aim to evaluate or explore alternative ways of delivering or organising a particular trial process. (<https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-019-3980-5> or <https://www.qub.ac.uk/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/SWATSWARInformation/Repositories/SWATStore/>)

5.4 Feasibility visits

Please note that once the project is recommended for funding, in collaboration with you and based on the feasibility data you provided, KCE in collaboration with a CRO may visit participating sites to check accrual commitments and predictions. This additional check does not mean that KCE takes any sponsor responsibility.

5.5 KCE sponsor visits

By submitting a research proposal under the KCE 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 sponsor on-site visit.

5.6 Data protection

By submitting a research proposal under the KCE Trials programme, each candidate investigator and sponsor team 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 investigator and sponsor on upcoming activities under the Trials programme
- (iii) to use your data anonymously to perform statistics

By submitting a research proposal under the Trials programme, each candidate investigator and sponsor acknowledges and accepts that said 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 said 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 said 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@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.

5.7 Data transparency

By submitting a research proposal under the Trials programme, each candidate investigator and 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, if their proposal is selected.

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, protocol and clinical trial report may be shared with third parties and will be available on the KCE website.

Before submitting a new application, a candidate Sponsor/BCC should have made results publicly available³ for all previous trials funded by KCE that are past 12 months from primary study completion (the last visit of the last subject for collection of data on the primary outcome). If this condition is not met, KCE Trials will notify the investigator and the Sponsor/BCC who will have three months from then to comply.

³ At least by posting to the results section of the clinical trial registry

6. Links & downloads

Documents for trials with sponsor in Belgium

- 2024 Call text (pdf) version 1.0, 14 May 2024
- Research application form including guidance (Word) version 1.0, 24 Apr 2024
- Budget tool (Excel) version 6.3, 14 May 2024 + guidance (pdf) version 6.3, 14 May 2024
- Template support letter candidate sponsor (Word) version 1.5, 17 Apr 2024
- Template commitment letter party offering support (Word) version 1.3, 17 Apr 2024
- Research agreement template (Word) version 6.3, 14 May 2024
- IMP/MD Protocol template for Full Research Proposal (Word) version 3.0, 13 Apr 2023
- Non IMP/MD Protocol template for Full Research Proposal (Word) version 1.0, 14 Apr 2023
- Top ten tips and tricks for a successful research outline (pdf) version 3.4, 22 Apr 2024
- [Answers to frequently asked questions](#)
- [Resources for investigators](#)
- What is a SWAT: <https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-019-3980-5>
- Patient involvement plan (Word) version 2.0, 24 Apr 2024

Documents for trials with international sponsor

- Budget tool international trials (Excel) version 5.3, 14 May 2024 + guidance (pdf) version 5.3, 14 May 2024
- Template support letter Belgian coordinating centre (Word) version 1.4, 17 Apr 2024
- Template commitment letter international sponsor (Word) version 2.4, 17 Apr 2024
- Research agreement template BCC (Word) version 5.2, 11 Apr 2024

7. Contact and further information

For further information on the KCE Trials programme and the 2024 investigator-led call, please consult the KCE website <https://www.kce.fgov.be/>.

For any questions, contact us at trials@kce.fgov.be.

Annex I

Evaluation criteria investigator-led call 2024

Sponsor and research team	<ul style="list-style-type: none"> • There is a representative distribution of recruiting sites. Minimally participating centres include one centre from each region (Flanders, Brussels, Wallonia), unless there is a good justification not to do so, as explained in the submission. • The sponsor and the CI have no conflict of interest in regards with the performance and the possible results of the trial and ensure that their team and collaborators do not either. • The sponsor's team has the necessary skills, capacity, procedures and experience in conducting non-commercial multicentre trials and has the ability to comply with all sponsor related obligations. There is sufficient support from a clinical trial centre or equivalent. 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.
Design	<ul style="list-style-type: none"> • The study design would answer the research question proposed. • The trial design is pragmatic. • Trial design should allow for sufficiently long follow-up. • A randomised, multicentre design is mandatory. • Sample size should be correct and well justified. • The use of centralised randomisation and e-CRFs are mandatory. • Only a limited set of variables, needed for the pre-planned analyses, are to be collected. All variables collected need to be well justified. • The design and data collected allow for possible health-economic analysis.
Need for Evidence	<ul style="list-style-type: none"> • 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 value for money for the Belgian health care system	<ul style="list-style-type: none"> • 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. <p>Research outlines that contain insufficient information to judge the expected value for money will receive a low score.</p>
PICO	<ul style="list-style-type: none"> • The trial intervention(s) should reflect current clinical practice as close as possible. • The inclusion and exclusion criteria are well defined and reflect the real-world population for which the intervention is intended. • Outcomes are patient centred and include the core outcome set, if available.
Return on investment	<ul style="list-style-type: none"> • 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 outcomes) of the Belgian healthcare system, preferably without the need for an additional implementation project (see potential value for money).

Patient and public involvement	<ul style="list-style-type: none"> • KCE strongly encourages patient involvement in research. The involvement of patients and/or the 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 (see patient involvement document). • A lay summary of the study in English should be included.
Timelines and feasibility	<ul style="list-style-type: none"> • The duration of the study is realistic and will preferably generate results within five (5) years. An extension of the follow-up period after the primary outcome is included if needed. • The risk of recruitment delay is considered low. The number of participating sites is sufficiently high and the investigators have access to a sufficient number of eligible participants 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 participant recruitment. The investigators allow KCE to verify these requirements during a study site visit. • The relevance of the trial results at the time of publication should be justified.
Implementation	<ul style="list-style-type: none"> • The trial results can have an immediate and important impact on the efficiency of the Belgian healthcare system, without the need for an additional implementation project.