KCE TRIALS PROGRAMME

KCE Trials 2021 Investigator-led call

Call text

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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. comparison between medication and surgery, between different surgical techniques, between lifestyle changes and a medical intervention, 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 in use in clinical practice in a given indication, but are not yet sufficiently directly compared (i.e. which of the two treatment options work best in daily practice).** Since 2015, KCE is managing a national funding programme of such pragmatic practice-oriented clinical trials, the KCE Trials Programme. The annual budget is 9.5 € Million. To date, 34 clinical trials have been selected within this programme (see funded trials for more information on these trials or our dynamic dashboards for progress in recruitment).

This 2021 investigator-led call is the 6th national call of KCE Trials on comparative effectiveness (see calls for more information on other past and present calls). The 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 are not limited to drugs or medical devices but also include a broad range of 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.

2. CRITERIA

2.1 Who can submit to the 2021 investigator-led call?

This call is investigator-led, meaning that investigators who submit a research outline should have the support of a non-commercial sponsor to perform the trial. It is strongly recommended that trials are developed and conducted with the assistance of a clinical trial unit or equivalent. Only multi-centre 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 participating investigators in the three regions.

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 this 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 qualify as non-commercial sponsor under the applicable laws, including the law of May 7, 2004 related to experiments on human person. 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, both using the KCE Trials templates, should be included.

For international trials with a Belgian sponsor and with more than 10% of patients recruited abroad, participation of other funders in the sponsor and site costs will be required.

2.2 Scope

Inclusion criteria

The primary aim of the study is non-commercial (see Belgian law on experiments on human persons of May 7, 2004).

- The candidate sponsor (and the BCC, if applicable) qualifies as a non-commercial sponsor under the applicable laws, including the law of May 7, 2004 related to experiments on human persons, or equivalent if the sponsor is not located in Belgium.
- The holder of the intellectual property rights on the studied intervention or comparator to which the experiment relates is neither directly nor indirectly the sponsor of the experiment.

- The sponsor exercises the intellectual property rights to the concept of the experiment, its implementation and the scientific data resulting from it.
- The funding granted under the research agreement complies with the European state aid regulations.

Design

- The trial is randomised (at individual level or in clusters) and multi-centric (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 a given 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) is considered in scope. A change of timing, e.g. first line versus second line, or change in dosing or duration of the treatment are also considered in scope.
- Studies on the effect of medical devices, tools or *on patent* drugs are in scope, provided that there is a strong justification why the study would not be performed by the marketing authorisation holder or manufacturer, and provided there is a high return on investment expected.

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 3 conditions are met:
    - The drug is off-patent.
    - There is a potential for high return on investment.
    - There is substantial underlying evidence that supports moving to a large-scale confirmatory randomised trial.

Exclusion criteria for the 2021 call

Started studies

- Studies for which recruitment has already started in Belgium, or which have already been submitted to a Belgian ethics committee 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 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 used already 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 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 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 (5) years. A long term follow-up study after collection of the primary outcome can be included if appropriate.

For the budget of the proposed trial, no maximum amount is defined. However 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).

2.4 Patient and public involvement

KCE strongly encourages patient involvement in research. The involvement of patients and/or public in the development of the project (e.g. 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.

2.5 Selection and prioritisation criteria

The detailed selection criteria for the 2021 call are listed in Annex I.

Proposals will be evaluated based on the information available in the submission. Applicants should make sure that sufficient and 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

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, and/or the expected effect of the intervention is large.
- 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

Trials can lead to increased efficiency of the health care system in addition to benefit for patients in the following ways:

- If positive, the trial may lead to savings for healthcare payers based on the trial results; while patient benefits remain 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 18th May 2021 until 13h on 14th September 2021.
- 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) at a later stage.
- We suggest to contact KCE Trials (trials"at"kce.fgov.be) in advance if you want to resubmit a proposal that was not selected 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 not yet done so. 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 legal advisor, clinical trial unit or equivalent early in the process and give them also access to your application.
- A detailed budget should be submitted using the dedicated budget tool, f**or which separate guidance notes are also available**. It is advisable to complete the budget tool in collaboration with the clinical trial unit.
- All documents for the submission are detailed below in the "6. Links & downloads" section and can be found on our website.
- To be deemed valid and to enter the selection process, a submission should:
    - Be written in English.
    - Be submitted through the online submission platform before the deadline.
    - Include details of 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.
    - 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 or the contract should be included in the initial submission in order to assess the non-commercial nature of the trial. Simple purchasing on normal market condition does not require this signed commitment letter.
    - Include a clearly defined research question in the PICO format (Patients, Intervention, Comparator, Outcome).

4. Selection procedure

The evaluation and selection of research proposals comprises several steps:

1. All research outlines received will be assessed for whether or not they are within the scope of the 2021 call as defined in this call text.
2. 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. A maximum of 20 proposals will be discussed by the Panel. If more research outlines are received, the research outlines with a low score on prioritisation criteria and/or for the value for money criterion may be excluded at this stage.

3. Based on the Panel's scores, the KCE Trials Prioritisation Group will prioritise the most relevant research proposals for further evaluation. A maximum of 10 proposals will be forwarded to the Trials Board (TB).
4. Candidates will be informed about the results of the first steps of the selection procedure in December 2021.
5. Shortlisted research outlines that are considered highest priority will be evaluated for their methodological quality and scientific value by the Trials Board (TB). The first TB meeting for the 2021 call will be planned during the first quarter of 2022.
6. 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).
7. The evaluation of your proposal by the TB may involve several review cycles (see website). Proposals submitted to the 2021 investigator-led call can be recommended for funding by the Trials Board in March 2022 at the earliest. A proposal will be reviewed by the TB a maximum of five times.
8. 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).

More information on the selection process can be found here on the KCE website.

5. Financial and legal issues

5.1 Terms and conditions

By submitting a research proposal to the KCE Trials programme, 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 is allowed if accepted by KCE. The Co-Funder or commercial entity should accept all the principles set forth in the KCE Trials research agreement template and contracts need to be reviewed for approval by KCE Trials.

If candidate research teams have major comments on the research agreement, this should be discussed with the KCE Trials team before submitting a proposal. In that case and if agreed between both parties, the template with comments in tracked changes should be attached to their submission.

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 Full Research Proposal (FRP) 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"at"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 following items:

- The sponsor costs
- The site costs
- For justified qualitative research (process evaluation of complex interventions) and Studies Within A Trial (SWATs[1]) a limited budget can be included.

[1] 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)

For some studies a pilot or feasibility study will be warranted by KCE Trials for which a separate budget will be foreseen in due course. For international trials the budget will depend on, amongst others 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 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.

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 patient 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. patient randomisation, trial report, etc.). Follow-up of milestones and payments will be coordinated by the KCE Trials team.

5.3 Feasibility visits

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

5.4 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.

5.5 Data protection

By submitting research proposals 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 sponsor on upcoming activities under the Trials programme
- (iii) to use your data anonymously to perform statistics

By submitting research proposals 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"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.

5.6 Data transparency

By submitting research proposals 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 and protocol may be shared with third parties and will be available on the KCE website.

6. Links & downloads

Documents for trials with sponsor in Belgium

- 2021 Call text (pdf) version 1.2, 04 June 2021 and Overview important dates (pdf) version 1.0, 24 February 2021
- Research application form including guidance (Word) version 1.2, 11 May 2021
- Budget tool (Excel) version 6.0, 15 May 2021 + guidance (pdf) version 6.0, 18 May 2021
- Template support letter candidate sponsor (Word) version 1.2, 10 May 2021
- Template commitment letter co-funder (word) version 1.0, dated 12 May 2021
- Research agreement template (Word) version 5.1, 03 June 2021
- Protocol template for Full Research Proposal V2.2 (Word) 13 Aug 2020
- Top ten tips and tricks for a successful research outline (pdf) version 3.1, 11 May 2021
- 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 document (pdf) version 1.0, 12 May 2021

Documents for trials with international sponsor

- BCC Budget tool (Excel) version 5.0, 20 May 2021 + guidance (pdf) version 5.0, 18 May 2021
- Template support letter national coordinating centre version 1.1, 7 May 2020
- Template commitment letter international sponsor version 2.1, 7 May 2020
- Research agreement template BCC (Word) version 4.0 dated 03 June 2021

7. Contact and further information

For further information on the KCE Trials programme and the 2021 investigator-led call, please consult the KCE website https://www.kce.fgov.be/.

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

Annex I

Selection criteria investigator-led call 2021

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 value for money 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 value for money will receive a low score.

PICO	• The trial is a non-commercial comparative effectiveness trial, comparing two interventions with 'no treatment' being one of the possible treatment options that are already in use in Belgium in a given indication, without limitation in terms of therapeutic domain or type of intervention or comparator.
	• 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) is considered in scope. A change of timing, e.g. first line versus second line, or change in dosing or duration of the treatment are considered in scope.
	• Interventions that have been used only within the framework of clinical research (including pilot studies or feasibility studies), are out of scope.
	• Medication used off-label in daily practice for a given indication is considered in scope.
	• If the trial is a repurposing trial, 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 randomised trial.
	• 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.

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 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.
Return on investment	• 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 potential value for money).
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 (see patient involvement document). • A lay summary of the study in English should be included.
Sponsor and research team	• Participating centres include at least one centre from each region (Flanders, Brussels, Wallonia), unless there is a good justification not to do so. • The sponsor (and Belgian Coordinating Centre if applicable) 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 exercises the intellectual property rights to the concept of the experiment, its implementation and the scientific data resulting from it. The holder of the patent on a medicinal product or of a registered trademark for a medical device to which the experiment relates is neither directly nor indirectly the sponsor of the experiment. • 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 related to experiments on human persons. There is sufficient support from a clinical trial unit 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. • The agreement must comply with the European state aid rules and regulations.
Timelines and feasibility	• 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 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 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 is accepted by the sponsor.