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

KCE Trials
Fast-track rolling call for clinical studies on Covid-19

Call text

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1. Background

In response of the urgent need for clinical research into covid-19, KCE Trials is organising a rolling call for proposals for covid-19 clinical trials, using a fast-track procedure for selection (4 weeks after submission). The call is for rapid response proposals i.e. studies that should be up and running within the next months. It is a rolling call, meaning that the selection process starts upon submission and that there is no fixed closing date (the tentative closing date of the call, October 15th 2020 13.00, may be prolonged depending on availability of funding next year). The existing KCE Trials selection process is adapted and simplified to be used to select, fund and follow-up 'rapid response' COVID studies. The high-level process can be found below.

This fast-track covid-19 rolling call focuses on non-commercial multi-centre randomised interventional (therapeutic or diagnostic intervention) trials, where there is a high and urgent need for generating evidence for covid-19 patients, and where there is substantial underlying evidence that supports performing a large-scale confirmatory randomised trial. Typical examples of trials in scope are drug repurposing studies of old (off patent) medication that could help treat covid-19. Trials including newer drugs (on patent and already on the market) are also in scope, provided the Sponsor has a strong justification why the study should/would not be performed by the market authorisation holder. Trials on drugs still in development are out of scope. Interventions are not limited to drugs and devices, diagnostic trials with clinically relevant endpoints for the management of Covid-19 are also in scope, as are interventions related to the rehabilitation of covid-19 patients. The aim of the study cannot be commercial, and the sponsor should be a non-commercial sponsor, in Belgium or abroad (in that case KCE Trials funds the coordination of the study in Belgium for the participation of Belgian centres).

A well-justified reason for an accelerated review process is required. This fast-track covid-19 rolling call is open in addition to the KCE Trials annual investigator-led call for studies (link call 2020), so trial proposals for non-urgent COVID-19 research questions can be submitted under the 2020 KCE Trials call (closing on September, 15th), provided they are within the scope of the call, and will follow the selection procedure for that call. Information on previous KCE Trials calls can be found on our website, where you can also find details of our funded trials.

The funding of trials selected in this fast-track rolling call will not originate from the usual KCE Trials Programme budget, but will be decided on a case by case basis and will require specific approvals from the Federal Minister of Budget. The prolongation of this call is conditional to the availability of funding.

2. Criteria

2.1 Who can submit to the fast-track COVID-19 investigator-led rolling call?

This call will be investigator-led, meaning that investigators who submit a research proposal 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. Participating centres should include at least one centre from each region (Flanders, Brussels, Wallonia), unless there is a good justification not to do so. In order to support collaboration between centres and avoid duplication of research efforts, at least all academic hospitals (or academic centres for general practice or relevant public health institutes) in Belgium should be informed about the study proposal and invited to participate.

A letter of support 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, using the template provided by KCE Trials, should be included in the submission. The candidate sponsor should qualify as a non-commercial sponsor under the applicable laws (including the law of May 7 2004 if the sponsor is located in Belgium).

Participation of Belgian centres to an international non-commercial trial within the scope of this call, is also eligible for funding. In that case, the sponsor of the international trial should sign a commitment letter, confirming acceptance of the KCE Trials terms and conditions regarding the non-commercial nature of the trial and data sharing (see below). A signed letter of support by the Belgian coordinating centre, using the KCE Trials templates, should also be included in the submission.

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 of the call

The scope of this rapid response rolling call is limited to research questions concerning COVID-19 that need to be addressed urgently, and are supported by the relevant academic/research institutes/hospitals in the country and confirmed by the KCE Trials Prioritisation Group.

Inclusion criteria

Aim of the study

The primary aim of the study should be non-commercial (see Belgian law of May 7, 2004).

- The candidate sponsor should qualify as a 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 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 exercises the intellectual property rights to the concept of the experiment, its implementation and the scientific data resulting from it.
- The agreement must comply with the European state aid rules and regulations.

Design

- The trial is randomised (individual or cluster) and multi-centric (with ideally at least one recruiting centre in each region).

Intervention

- The trial compares two (or more) therapeutic interventions (drug, CE label device, other intervention. No treatment/test as comparator can be an option) with the aim of treating or diagnosing covid-19 patients.
- Drugs and devices should have market authorisation in Europe, the US or Japan (if the drug/device is not on the market in Belgium, the applicant has to explain how it will be made available to Belgian patients after the study).
- Diagnostic trials with clinically relevant endpoints for the management of Covid-19 are also in scope.

Specifically for trials where the intervention is an Investigational Medicinal Product (IMP),

- Studies on the effect of *off patent* drugs on covid-19 are in scope (drug repurposing studies, for drugs used off label), provided there is substantial underlying evidence that supports moving to a large-scale confirmatory randomised trial.
- Studies on the effect of *on patent* drugs on covid-19 (used off label) are in scope, provided that there is a strong justification why the study should/would not be performed by the market authorisation holder, and provided there is a high return on investment.

Exclusion criteria for the fast-track COVID-19 rolling call

Ongoing/ already started studies are out of scope

- Studies where recruitment has already started, or which have already been submitted to an ethics committee or to the FAMHP (Federal Agency for Medicines and Health products) are out of scope. There may be exceptions to this rule for international studies that have already started in other countries (to be discussed case by case).

Implementation studies and quality improvement studies are out of scope

- 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 guidelines or quality of care are also out of scope.

Pilot studies are out of scope

- There should be substantial underlying evidence that supports moving to a large-scale confirmatory randomised trial.

Development and innovation studies are out of scope

- Drugs and devices without market authorisation (Europe, or US, or Japan) are excluded.
- Devices without CE label are excluded.
- Software and apps used as part of the intervention should be fully developed, piloted and meet all regulatory requirements on data protection. 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.

2.3 Budget and duration of proposed trial

The duration of the study should be realistic and be able to generate first interim results preferably within 12 months. A long term follow-up study after collection of the primary outcome can be included if appropriate.

For the budget of the proposed trials, 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 Selection and prioritisation criteria

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.

Study proposals will be prioritised based on:

- the need for evidence in clinical practice
- the fact that funding by a commercial stakeholder is unlikely and/or not warranted
- the fact that the answer to the research question will not be available soon, as assessed by providing details of existing running clinical trials on the research question and their planned date of completion
- the geographical spread of the participating centres being well balanced over the different regions.

In addition, possible efficiency improvements for the Belgian health care system will be evaluated. 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.

3. How to submit?

- The call will be open to submissions starting from the publication day until it is closed, provisionally 15th October 2020 1PM. If the closure date is not 15th October, information on the closure date will be posted on the KCE website by this date and at least 2 weeks before closure.
- In order to save time and limit the number of review cycles, the candidates are asked to submit a full research proposal (FRP) (with a draft study protocol).

- 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. Once you can access the submission system, you will 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. Note that the application form is a copy of the application form used in the annual 2020 call. Fields that differ for this rapid call are indicated in green in the guidance note.
- Only the chief investigator can start and submit an application. 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 contact, 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, for which separate guidance notes are also available.
- 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 while the call is open.
    - 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.
    - 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 proposals received will be assessed for whether or not they are within the scope of the fast track COVID-19 2020 rolling call as defined in this call text. Each time a proposal is submitted in the submission system, the KCE Trials Prioritisation Group will be requested to check if the proposal is in scope (proposals that are clearly out of scope will not be advanced immediately to the PG) and to judge the priority of the research proposal for further evaluation within 5 working days using a written procedure followed by a videocall. Prioritised research proposals will immediately be forwarded to the Trials Board (TB). Candidates will be informed about the results of this first step of the selection procedure.
2. Prioritised research proposals will then be evaluated for their methodological quality and scientific value by the Trials Board (TB) using a written procedure of 5 working days followed by a videocall.
3. The evaluation of the proposal by the TB may involve several review cycles (see website). Proposals submitted can be. A proposal will be reviewed by the TB a maximum of three times. At the end of the TB, the proposal will be either recommended for funding by the Trials Board (with or without changes) either declined. Candidates will be informed about the results of this step of the selection procedure.
4. There is no global budget foreseen for this call. After the first review of the TB (if positive), a request for funding to the national covid-19 provision will be launched. The funding of the study depends of the positive response of that demand.
5. A contract will be signed after the following conditions are met: positive evaluation of the feasibility of the study, agreement on the budget, funding for the study is secured and the Board of directors KCE has approved the study.

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 can 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 international trials the budget will depend on, amongst others things, the Belgian contribution to the study.

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

The chief investigator should give as good a justification of feasibility as possible in their submission and provide available supporting data. Feasibility will be judged on this and other available information. No formal additional feasibility visits are planned.

5.4 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.

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.

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

- Research application form and guidance (Word) version COV1.0, 2 Jun 2020
- Budget tool (Excel) version 5.0, 11 May 2020 + guidance (pdf) version 5.0, 11 May 2020
- Template support letter candidate sponsor (Word) version 1.1, 7 May 2020
- Research agreement template (Word) version 4.0, 11 May 2020
- Top ten tips and tricks for a successful research outline (pdf) version 3.0, 22 May 2019
- Answers to frequently asked questions
- Resources for investigators

Documents for trials with international sponsor

- Budget tool international trials (Excel) version 4.0, 11 may 2020 + guidance (pdf) version 4.0, 11 May 2020
- 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 version 3.0, 11 May 2020

7. Contact and further information

For further information on the KCE Trials programme, please consult the KCE website. For any questions, contact us at trials"at"kce.fgov.be.