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

# KCE Trials 2018 Investigator-led call

# Call text

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# 1. BACKGROUND

Many questions in healthcare are currently not or 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, etc. KCE concluded in the summer of 2015 that public funding of such trials would be beneficial (Report 246-2015) under certain conditions. These trials not only contribute to better patient care but also to a more efficient use of public resources.

The Minister of Public Health Maggie De Block decided in the autumn of 2015 that KCE should launch and manage a programme of pragmatic practice-oriented clinical trials.

The KCE Trials programme, including the 2018 call, focuses on comparative effectiveness trials which show clear value for money and have the potential for return on investment. 'Comparative effectiveness ' studies compare two treatment options (including no treatment) 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). Accepted study interventions are not limited to drugs or medical devices but also include a broad range of interventions for example psychotherapy, diet, diagnostic tests or surgery.

Two previous calls have been previously opened: the 2016 commissioning call, the 2017 investigator-led call. In addition, a joint call with ZonMw from the Netherlands was launched earlier this year. Info on previous calls can be found here (https://kce.fgov.be/en/closed-calls), with details of funded trials here (https://kce.fgov.be/en/kce-trials/funded-trials).

# 2. CRITERIA

## 2.1 Who can submit to the 2018 investigator-led call?

This call will be investigator-led, meaning that investigators who submit a research outline should have the support of a non-commercial sponsor to perform the trial. Preferably, trials are conducted with the assistance of a clinical trial unit or equivalent.

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.

## 2.2 Budget and duration of proposed trial

For the budget of the proposed trials, no maximum amount is defined.

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.

The duration of the study should be realistic and be able to generate results preferably within five (5) years. An extension of the follow-up period after the primary outcome can be included.

## 2.3 Scope

**Inclusion criteria**

Comparative effectiveness

- The trial is a comparative effectiveness trial, comparing two interventions (including no treatment) that are already in use in Belgium in a given indication. Medication used off-label in daily practice is considered in scope.
- Repurposing of drugs for an intervention 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 of high return on investment.
    - There is substantial underlying evidence that supports moving to a large-scale confirmatory randomised trial.

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

- The candidate sponsor should qualify as non-commercial sponsor under the applicable laws, including the law of May 7, 2004 or equivalent e.g. if the sponsor is not located in Belgium.
- The holder of the patent of a medicinal product or of a registered trademark of a medical device to which the experiments relate is neither directly nor indirectly the sponsor of the experiment.
- The sponsor exercises the intellectual property rights to the concept of an experiment, its implementation and the scientific data resulting from it.
- The agreement should be in line with the European state aid rules and regulations.

**Exclusion criteria for the 2018 call**

Implementation studies

- Implementation Research, defined as "the scientific study of methods to promote the uptake of research findings in practice". Interventions that aim to improve implementation of guidelines or quality of care are out of scope.

Development and innovation studies.

- Drugs and devices should have market authorisation in Belgium; for off-label use and repurposing the conditions are set out above (see inclusion criteria). Software and apps used as part of the intervention should be fully developed and piloted. All types of interventions including interventions related to organisation of care, should already be in use in practice, outside the framework of research.

Started studies

- 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.

## 2.4 Selection criteria

The detailed selection criteria for the 2018 call are listed in Annex I.

Applicants should make sure that sufficient information is available in their submission to evaluate the submission according to the listed criteria.

Study proposals will be prioritised based on the need for evidence in clinical practice and possible efficiency improvement for the Belgian health care system. 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 from 5th June, 2018 until 13h on 25th September, 2018.
- 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.
- All submissions must be done using the dedicated application form. A guidance document on how to complete the application form is available. The deadline for the completion of the application form and all applicable attachments is **on 25th September 2018 13h**. KCE Trials is currently implementing a web-portal for applicants to submit their application electronically. This portal will open during the course of August; a mailing will be sent to the Trials Mailing list with effective date. In the meantime, applicants are encouraged to prepare their application using the word application form available on our website.
- A detailed budget should be submitted using the dedicated budget tool, for which separate guidance notes are available.
- All documents for the submission are detailed in section 6 and can be found on our website.
- To be deemed valid and to enter the selection process, a submission should:
    - Be received before the deadline of 13h on 25th September 2018
    - Contain all necessary information in the application form and budget template
    - Include details of chief investigator and candidate sponsor
    - Include a sponsor support letter: 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. The candidate sponsor should qualify as non-commercial sponsor under the applicable laws, including the law of May 7, 2004 if the sponsor is located in Belgium. If the sponsor is located abroad, a signed commitment letter by the international sponsor and a signed letter of support by the Belgian coordinating centre should be included.
    - 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 2018 call.
2. Research outlines that are within scope will be scored by a panel of clinical experts, health economists and representatives of patients and the public for their relevance and importance for the Belgian health care system. Based on the Panel's scores, the KCE Trials Prioritisation Group will prioritise the most relevant research proposals for further evaluation. A maximum of 15 proposals will be forwarded to the Trials Board (TB).
3. Candidates will be informed about the results of the first steps of the selection procedure in December 2018 at the latest (no individual feedback will be provided).
4. 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 2018 call is planned early in December.
5. For outlines that are shortlisted for the full research proposal (FRP) stage (or resubmission of a research outline) during the TB meeting in December, the sponsor team will have at least 8 weeks to develop and submit their FRP (including a draft study protocol). To further support the selected applicants in developing their proposal, a strengthening workshop will be organised on 17th December 2018. We expect the chief investigator and a representative of the research team to be present.

6. The evaluation of your proposal by the TB may involve several review cycles (see website). Proposals submitted to the 2018 investigator-led call can be recommended for funding by the Trials Board in April 2018 at earliest and in December 2018 at the latest.
7. For this call, we expect that 5 to 10 trials will be funded.

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 version 2.0 that can be found on the website. 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. Candidate investigators are strongly advised to contact the legal department of the sponsor timely.

Please note that KCE shall remain entitled at all times to postpone, suspend and/or withdraw any research call (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 submission at any time before signature of the research agreement with KCE.

Questions and any possible complaints regarding decisions of the TB, PG 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 Ownership of project results

Results and new Intellectual Property Rights (IPR) resulting from projects funded through the KCE Trials programme will be owned by the Sponsor and/or any of its partners. Since the main purpose of the KCE Trials programme is to generate results that will serve the general public interests, and specifically the interests of the patients and health care payers, the Sponsor and any of its partners will:

a. not knowingly or directly exploit the results arising from the study (including any and all trial data and any and all IPR arising therefrom, trial report, etc.) in any way that is or could be detrimental to such interests;
b. use best efforts to disseminate the trial results by disclosing them to the public by appropriate means, including in scientific publications and
c. provide a full access right of the trial data to KCE. This access right will be non-exclusive, worldwide, irrevocable, unlimited, royalty-free and transferable, including the right to sub-license, for any non-commercial research purposes, public health care services purposes, and/or for designing, evaluating, and/or implementing policies or programmes in connection with or related to health care, health economics, pharmacoeconomics and/or social security.

In accordance with the principles set forth above, the commercialization of the results is not and should never be the main aim of the Sponsor.

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.

### 5.3 Budget

The budget of 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.

Please note that once the budget is agreed upon, 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 costs in the payment schedule will be paid on the basis of patient visits completed as planned. Usually, about 20% of the budget will be paid for the first milestone (e.g. signature of research agreement or grant letter), 5% to 10% for the trial report and a final 5% when the scientific publication has been submitted. The rest of the money is split based on accrual milestones. Follow-up of milestones and payments will be coordinated by the KCE Trials team.

## 6. Links & downloads

- Research application form (Word) v1.0 + guidance (pdf)
- Budget tool (Excel) v3.0 + guidance (pdf)
- Budget tool international trials (Excel) v2.0 + guidance (pdf)
- Template support letter candidate sponsor
- Template support letter national coordinating centre
- Template commitment letter international sponsor
- Research agreement template version 2.0 (Word)
- Timelines
- Top ten tips and tricks for a successful research outline
- Answers to frequently asked questions
- Resources for investigators

## 7. Contact and further information

For further information on the KCE Trials programme and the 2018 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

## Selection criteria investigator-led call 2018

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

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