Belgium-Netherlands Funding of International Trials

Third Call

Call text

May 2023

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1. BACKGROUND

In 2017 KCE and ZonMw launched the joint program Belgium-Netherlands Funding of International Trials (**BeNeFIT**). In this initiative, a new funding selection process was developed that integrates approaches from both organisations. The main focus of the program is to provide funding for non-commercial practice-oriented research that is immediately relevant to patients, caregivers and policymakers in Belgium and the Netherlands and is conducted in collaboration by institutions from both countries.

In clinical practice, many treatments have not been thoroughly evaluated, making it unclear whether a patient benefits from a particular treatment, or which treatment is actually preferable. Evaluation of clinical practice is relevant to health care stakeholders in Belgium and the Netherlands and by working together, clinical evaluation trials can be carried out more quickly and efficiently.

Health care efficiency research compares the effectiveness and cost-effectiveness of treatments that are part of health care in daily practice. Studies are focused on health benefits for the patient, but also evaluate costs. In Belgium the government finances these studies through KCE and in the Netherlands funding is provided by the ZonMw programs 'Efficiency Studies' and 'Rational Pharmacotherapy', commissioned by the Ministry of Health, Wellbeing and Sports.

In September 2022 the Belgian Health Care Knowledge Centre (**KCE**) and The Netherlands Organisation for Health Research and Development (**ZonMw**) agreed to invest 9 million euros in the third call of the BeNeFIT program.

2. AIM OF THE CALL

The aim of the call is to provide funding for clinical trials that compare the effectiveness of existing health care interventions that are already in use for a given indication, e.g. comparisons between two medications, medical therapy versus surgery, trials investigating optimal timing of surgery etc. The research should be pragmatic and practice-oriented.

Trials funded within the BeNeFIT program must be of non-commercial nature. The different treatment options that are compared in a BeNeFIT trial should concern treatments that are (or have the potential of being) reimbursed by health care payers in Belgium and the Netherlands. Moreover, each BeNeFIT trial should have the potential of generating results with an immediate and important impact on the efficiency of the health care systems in Belgium and The Netherlands.

3. CRITERIA

3.1 Who can submit to the BeNeFIT call?

Research teams from institutions in Belgium and the Netherlands can apply to this call. The sponsor* (the main applicant, who shall also be the sponsor of the trial under ICH/GCP) should be located in one of the two countries and should be supported by a national coordinating centre in the other country**. Both Belgian and Dutch centres should participate, ideally with a good regional spread.

** As defined in ICH-GCP*

***In case of co-sponsorship: co-sponsors must enter into an agreement that complies with applicable laws and the provisions of the Terms and Conditions of the Third Benefit Call. All co-sponsors will be jointly and severally liable towards the Funding Agencies for the compliance with the provisions of these Terms and Conditions and (if applicable) with the provisions of the research agreement that incorporates them. In case of co-sponsorship, one co-sponsor must act as main applicant.*

Belgium

- In Belgium, the sponsor or the national coordinating centre should qualify as non-commercial sponsor under the applicable laws, including the Belgian law related to experiments on human people (May 7th, 2004).
- Participating centres should include at least one centre from the Flemish and the French speaking part of the country[$].
- The funding granted under the research agreement complies with the European state aid regulations.

The Netherlands

- In the Netherlands, the sponsor or the national coordinating centre must be a research organisation or care institution[α].
- At least one of the participating institutions in the Netherlands should be a non-academic hospital[$].
- Studied interventions should be (or have the potential of being) reimbursed under the "Basic Health Care" Act and/or the "Long Term Care" Act packages ("basispakket Zorgverzekeringswet" and "Wet langdurige zorg") in The Netherlands.
- Studies should fall within the scope of the "Efficiency Studies" (DoelmatigheidsOnderzoek) program or the "Rational Pharmacotherapy" (Goed Gebruik Geneesmiddelen) program of ZonMw. For detailed information please consult the websites of ZonMw for 'Efficiency Studies' and 'Rational Pharmacotherapy'.
- No grants will be awarded by ZonMw if this would or could constitute unlawful State aid. Therefore, the following State aid measure applies to this funding round: Exemption Decision for Services of General Economic Interest (**SGEI**). For the purposes of this call for grant applications, ZonMw will consider proposed project activities as SGEI. This means that there are specific conditions for funding and rules for budgets. You can find out more about the SGEI Exemption Decision in Annex III.

A national coordinating centre must be assigned in the country where the sponsor (main applicant) is not located. The national coordinating centre is responsible for coordinating the trial in close collaboration with the sponsor. Tasks assigned by the sponsor to the national coordinating centre may include managing the submission of the trial to the applicable bodies and translating and adapting documentation for its respective country.

The sponsor and the national coordinating centre have to submit a letter of commitment, using the appropriate template and signed by the legal representative of the institution, together with the application.

Participating centres in other countries are allowed if co-financing is provided. Funding of centres outside of Belgium and the Netherlands cannot be included in the BeNeFIT budget.

3.2 Budget and duration of proposed trial

For both the budget and duration of the proposed trial 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 total assessment procedure. The duration of the study should be realistic. The available budget for this call is 9 million euros.

[$] *If not possible, please justify.*

[α] *Definition (Framework for State aid for research and development and innovation (2014/C 198/01) paragraph 15 sub ee): research organisation (onderzoeksorganisatie) and care institution (zorginstelling) (artikel 5, lid 1, wet toelating zorginstellingen).*

3.3 Scope

The BeNeFIT call focuses on comparative effectiveness trials which show clear value for money and have the potential for return on investment (see Annex 1: Selection and prioritization criteria).

Comparative effectiveness trials compare the benefits and harms of different treatment options that are already in use in the health care system for the given indication but which have never been adequately compared directly (*i.e.* which of 2 treatments work better in daily practice). Studied interventions must already be in use in daily practice for the studied indication in both countries. Accepted trial interventions are not limited to drugs or medical devices but also include a broad range of interventions, such as psychotherapy, diet, diagnostic tests or surgery. No treatment or placebo are also accepted as trial interventions. Proposals will be selected based on the need for evidence in clinical practice, possible efficiency improvement and potential return on investment for the health care systems.

The primary aim of the trial must be of non-commercial nature. In addition, the holder of the Intellectual Property Rights (**IPR**) 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 IPR to the concept of the experiment, its implementation and the scientific data resulting from it.

The trial should have a randomised (at individual level or in clusters) and multi-centre design.

Out of scope (see Annex I (9.1.2):

- 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.
- Health services research that studies the organisation of care (at macro, meso or micro level). This call offers no scope for research involving organizational innovations, such as task rearrangement, offering the intervention at another location or logistical organization of care.
- Interventions that have been used only within the framework of clinical research or pilot testing are out of scope.
- Studies of medicinal products or medical devices that are not marketed in Belgium and the Netherlands. Devices should have a CE label. Off-label use that is well established in usual care is accepted.
- Prevention, screening (early detection) or tests to predict risk or response. An exception is healthcare-related prevention, including relapse prevention. Appropriate in this funding round are preventions that target a group of patients with an existing condition leading to complications, limitations, a lower quality of life or mortality.
- Studies that already have been submitted to authorities, ethical committees and/or have already started recruitment.
- Interventions that are not eligible for possible reimbursement in at least one of the two countries.

3.4 Evaluation criteria

Proposals will be evaluated for relevance and for scientific quality by the BeNeFIT Scientific Evaluation Committee (**SEC**) (see section 4.1).

The evaluation criteria are listed in Annex I (9.1.3). Evaluation of the submission will be based on the information available in the submitted documents; applicants should make sure that sufficient information is available in their submission for the SEC members to evaluate the submission according to the listed criteria.

4. SELECTION PROCEDURE

4.1 Management Boards

Two boards, the Call Steering Committee (**CSC**) and the Scientific Evaluation Committee (**SEC**), will manage the evaluation process of the call with support of the call Secretariat (set up at ZonMw, the Netherlands). CSC and SEC members will not be part of research teams that apply to this call. Members' responsibilities include the evaluation of research outlines and full research proposals and the final selection and award of the trials.

- The CSC is composed of representatives from KCE and ZonMw. CSC members adhere to the Code for dealing with Personal Interests (CPI) policy. The CSC will supervise the organisation and progress of the call. The CSC will make the final decision on the recommended proposals to be funded, based on a ranking list provided by the SEC, the additional criteria (Annex I - 9.1.4) and the available budget.
- The SEC is a panel of internationally recognised scientific experts and patient representatives, responsible for the evaluation of submitted proposals. SEC members must sign a confidentiality form and report any potential conflicts of interest, in adherence with the Code for dealing with Personal Interests (CPI) policy. According to the code, appropriate control measures are taken in case of a potential conflict of interest.

4.2 Overview of the selection procedure

Proposals submitted to the BeNeFIT call will undergo a 2-step selection procedure:

1. The submission of an initial research outline (**RO**) outlining the key information on the research proposal;
2. Invitation to submit a full research proposal (**FRP**) for ROs shortlisted by the SEC and CSC.

4.3 Eligibility check and evaluation of Research Outlines

Submitted ROs will be checked for eligibility by the call Secretariat, according to the eligibility criteria listed in Annex I (9.1.1). ROs that do not meet the eligibility criteria will be declined without further review.

Eligible ROs will be assessed by the CSC on whether they are within the scope of the call (as defined in section 3.3). ROs that are out of scope will be declined without further review.

ROs that are eligible and in scope will be forwarded to a selection of SEC members that will evaluate the proposals for relevance and scientific quality in accordance with the criteria listed in Annex I (9.1.3). The SEC members will evaluate the ROs with a score between 1 and 5 for both relevance and scientific quality. The ROs with a minimum mean score of 2 on relevance and scientific quality will be ranked according to the mean scores on relevance. The 20 highest ranked proposals will be selected for evaluation during the SEC meeting. However, the CSC has the right to change the final selection based on the SEC ranking, in order to maintain a balance between funding sources. Moreover, there should be a minimum of 4 proposals with the main applicant residing in each country. ROs not forwarded to the SEC meeting will not be eligible for funding.

During the SEC meeting, the SEC will evaluate the ROs for relevance and scientific quality, based on the criteria listed in Annex I (9.1.3). After discussion, all individual SEC members will score the ROs with a score between 1 and 5 for both relevance and scientific quality. At the end of the meeting, the ROs will be categorized according to the prioritization matrix (Annex IV), and then sorted by mean score on relevance followed by mean score on scientific quality.

Further prioritization and selection by the CSC is based on the SEC ranking order, the additional criteria listed in Annex I (9.1.4) and available budget. In other words, highly ranked ROs (based on the scores by the SEC) may not necessarily be prioritized and selected. CSC decisions are taken in consensus, meaning that ROs that go to the next round have received approval from both KCE and ZonMw.

The number of ROs that will be invited to submit a FRP will be limited. The selection will be based on the available budget and aiming for an eventual success rate of around 50% of the FRPs received.

Invitation to submit a Full Research Proposal

All applicants will be informed by the CSC about the result of the evaluation process. Applicants of shortlisted ROs will be invited by the CSC to submit a FRP by the set deadline. The invitation letter may contain specific conditions and recommendations to take into account for the FRP. All conditions and recommendations should be sufficiently addressed in the FRP submission.

FRP submissions should include a draft protocol as attachment, including a patient information form. For the protocol, please use a protocol template (in English) as available on the website of the Dutch "Centrale Commissie Mensgebonden Onderzoek" (CCMO).

To further support the applicants in the development of their FRP, **a strengthening workshop** will be organised on **7 June 2023 AM**. We expect the main applicant and a representative of the coordinating centre located in the other country to be present.

4.4 Eligibility check and evaluation of Full Research Proposals

4.4.1 Eligibility check

The deadline for submission of the FRP is **5 September 2023 14:00h (CET).**

Submitted FRPs will be checked for eligibility by the call Secretariat according to the eligibility criteria listed in Annex I (9.1.1). FRPs that do not meet the eligibility criteria will be declined without further review.

4.4.2 External reviewer's evaluation, SEC member comments, feasibility study and right to reply (rebuttal)

Each retained FRP will be sent to a minimum of 3 external expert reviewers and a minimum of 3 SEC members for a written assessment on the relevance for clinical practice and scientific quality. External reviewers are international domain experts specifically selected for each FRP.

Both, the external reviewers and SEC members, will receive the FRP and will be asked to send their comments to the call Secretariat. All written reports of the external expert reviewers and SEC members will subsequently be sent to the main applicant.

In parallel, the CSC requests an additional feasibility study to be performed. In collaboration with the applicant and based on the feasibility provided in the FRP, a third party (CRO) appointed by the CSC will visit participating sites to check accrual commitments and predictions.

Applicants are entitled to request the CSC to support the development of the FRP and feasibility study through *ad hoc* funding of € 20.000 (including any overhead or applicable VAT). Requests will be evaluated by the CSC upon its own discretion.

Finally, during the execution of the feasibility study the CSC will review the proposed budget by using the budget tool. A meeting with the project team will be planned to discuss the suggestions on the budget by the CSC.

Each applicant will have the opportunity to respond to the (1) external reviewers' evaluation, (2) SEC members' comments, (3) feasibility study and (4) the budget comments by means of a written rebuttal. This stage allows applicants to comment on factual errors or misunderstandings that may have been committed by the reviewers while assessing their proposal and to reply to reviewers' comments and questions. At this stage, applicants also have the opportunity to submit a revised protocol and budget based on the feedback from the external reviewers, SEC members, and the outcome of the feasibility study. Deadline for submission of the written rebuttal, the feasibility report and the revised protocol and

budget is **15 January 2024 14:00h (CET).** Details on how to submit the requested documents will be communicated in due course.

4.4.3 Evaluation by the SEC

FRPs and the respective review reports, rebuttals and feasibility reports will be checked for completion and be sent to the SEC members for evaluation in preparation of the second SEC meeting.

The SEC will subsequently, after consideration of the evaluation criteria (see Annex I - 9.1.3), reviews, rebuttals, feasibility reports and their own discussions, give a score to each FRP for relevance and scientific quality. FRPs will then be ranked in a similar manner as the ROs, see section 4.3.

4.5 Funding decision

Based on the final scores for relevance and scientific quality, the CSC will take the final decision to recommend applications for funding, following the ranking order of the SEC and taking into account the prioritization criteria (Annex I – 9.1.4).

The contribution of each country and each Dutch funding program cannot exceed the amount attributed to the call by that particular country or program. No additional projects can be funded when one of the contributors has reached its budget limit during the prioritization process. Therefore, it is possible that a country will not spend its reserved budget. Also, if the contribution of one of the two ZonMw programs reaches its budget limit, no additional projects within the scope of that program can be funded (see section 4.3).

5. SUBMISSION PROCEDURE

5.1 Online portal

Proposals can only be submitted using the online submission portal of MijnZonMw. The **deadline** for the submission of Full Research Proposal is **05 September 2023 14:00h.** Practical information can be found in the manual.

In addition to files which are required to be attached to the submission, data need to be completed directly online in the submission portal. The full research proposal needs to be written using the specified questions in the submission portal. To complete the application, carefully read the guidance notes included in the online form. A detailed budget must be submitted using the dedicated budget tool, for which separate guidance notes are available. The completed budget tool needs to be uploaded as attachment to your online submission (both pdf and excel).

For technical questions, you can contact the ZonMw servicedesk via servicedesk@zonmw.nl.

For content related questions, please contact BeNeFIT@zonmw.nl or kce_trials@kce.fgov.be.

For questions related to the budget tool, please contact kce_trials@kce.fgov.be.

5.2 Budget

A standardised budget format is used in this call to allow careful evaluation of the budgets. Therefore, the budget of the proposal needs to be submitted using the specific budget tool for this call. The application form on MijnZonMw will require budget information, that can be directly copied from the Budget Tool ‘Application Form’ tab. Note that the budget information in the budget tool is considered prevailing.

The budget tool differentiates between costs that are considered as sponsor costs and site costs. Site costs can differ by country due to price differences and, more importantly, due to the number of recruited patients per country. To divide the budget and to help implementation, it is required to recruit patients in

both countries (and for Belgium with a good representation of Dutch and French speaking centres). ZonMw shall pay all costs in respect to a specific trial that were incurred in The Netherlands. KCE shall pay all costs in respect to a specific trial that were incurred in Belgium. If needed, the sponsor and national coordinator can agree to forward funding to the other country.

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. 15% at signature of research agreement or grant letter and 5% upon delivery of the data management plan, risk assessment plan and monitoring plan), 10-15% for the trial report and a final 5% when the scientific publication has been submitted. The rest of the money will be split based on accrual milestones. Follow-up on milestones and payments will be organised with the funding agencies.

6. FINANCIAL AND LEGAL ISSUES

6.1 Funding model

The BeNeFIT partners (KCE and ZonMw) have agreed to launch a joint call using the "virtual common pot" funding mode. This means that national funding will be made available through the national funding organisations according to national regulations. Once an applicant has been awarded funding for a proposal (the "**Sponsor**"), the partner from the country where the sponsor (main applicant) is located shall act as the main funding agency for the applicable BeNeFIT non-commercial trial (the "**Funding Agency**"). Applications will only be awarded if both BeNeFIT partners agree to fund.

6.2 Funding contracts

6.2.1 Terms and conditions

All trials granted and performed within this call are subject to the Terms and Conditions Third Benefit Call in accordance with the following:

- The main applicant or the national coordinating centre located in Belgium, shall sign a research agreement with KCE that incorporates the Terms and Conditions Third Benefit Call.
- For the main applicant or the national coordinating centre located in the Netherlands, the applicable grant conditions published on the website of ZonMw reflect the Terms and Conditions Third Benefit Call, as will be also stated in the award letter.

For the avoidance of any doubt, the BeNeFIT terms and conditions shall be identical for Belgian and Dutch applicants; only the manner in which these BeNeFIT terms and conditions are implemented (through a research agreement for Belgium and through grant conditions for the Netherlands) will differ.

Please note that KCE and ZonMw, the funding agencies, shall remain entitled at all times to postpone, suspend and/or withdraw any research call (even during the negotiation of the research agreement) upon their own discretion and that the funding agencies shall under no circumstances be obliged to select any pending FRP, enter into a research agreement or issue an award letter after FRP selection. Applicants can withdraw their submission at any time before signature of the research agreement from the Belgian funding agency or receiving the award letter from the Dutch funding agency.

6.2.2 Agreements

Consortium

Each trial will be performed by a consortium, consisting of the main applicant and the national coordinator in the other country.

The project consortium partners must sign a consortium agreement ("**CA**") for cooperation. The consortium partners are strongly encouraged to sign this CA before the official project start date, and in any case the CA has to be signed no later than six months after the official project start date. Upon request, this CA must be made available to the concerned funding agency.

In this call, no grant will be awarded if arrangements between the consortium partners would or could lead to the provision of unlawful State aid. The consortium agreement must follow the provided template. It is required for the FRP phase to have the intellectual property (**IP**)/contract specialist from both the main applicant and the national coordinator, review the draft consortium agreement template. While we expect that you agree to the terms of the consortium agreement template, you are welcome to provide comments. Any comments or remarks regarding the draft consortium agreement template can be attached as a separate document in the FRP application. The funding agencies reserve the right to assess this draft for compliance with the European law on State aid and Terms and Conditions Third Benefit Call.

Co-financing

Co-financing is possible, but any co-financer of the study will need to submit a signed letter of commitment. Applicants will need to submit an agreement with the co-financer after funding has been granted. The funding agencies reserve the right to assess this agreement for compliance with the European law on State aid and Terms and Conditions Third Benefit Call.

In your FRP application, you will describe who holds the rights to the existing knowledge (background intellectual property) that will be brought to the project. If you have any questions on this matter, contact your IP/contract specialist, who is likely to work at your organization's valorisation department or technology transfer office (**TTO**). It is advised to involve this person in your application at the earliest possible stage. The FRP (not the RO) will include the contact details of the IP/contract specialists from both the sponsor and the national coordinating centre.

Ownership of project results

Results and new IPR resulting from projects funded through the BeNeFIT call will be owned by the sponsor and/or coordinating centre and/or their collaborators. Since the main purpose of the BeNeFIT call 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 consortium partners will:

- 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;
- Use best efforts to disseminate the trial results by disclosing them to the public by appropriate means, including in scientific publications;
- Provide a full access right of the study data to each of KCE and ZonMw, the funding agencies. 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 programs in connection with or related to health care, health economics, pharmaco-economics and/or social security.

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

Co-funding is allowed under the condition that the co-financer accepts the relevant conditions set forth in the Terms and Conditions Third Benefit Call.

Collaborating Parties

(Applicable for Dutch applicants only)

A Dutch applicant and collaborator(s) will need to enter into service agreements on market-based and transparent conditions in order to comply with European State aid regulations. The conditions of the service agreement will need to be such that the applicant will be able to meet the obligations of the grant conditions such as (free) accessibility for further research, education and application, including an up-front transfer of any results generated by a collaborator to the applicant. The funding agencies reserve the right to assess this service agreement for compliance with the European law on State aid and Terms and Conditions Third Benefit Call.

7. LINKS & DOWNLOADS

- Mijn ZonMw application portal
- Mijn ZonMw manual for applicants (PDF)
- Guidance Budget tool (PDF)
- Budget tool (Excel)
- Estimation of potential revenues (Excel)
- Template letter of commitment sponsor (Word)
- Template letter of commitment coordinating centre (Word)
- Template letter of commitment co-financer (if applicable) (Word)
- Explanation Code for dealing with Personal Interests (PDF)
- Code for dealing with Personal Interests (PDF)
- Timelines (PDF)
- Terms and Conditions Third BeNeFIT Call (PDF)
- Consortium agreement template (Word)
- Feasibility template
- Frequently Asked Questions HTA
- Dutch "Centrale Commissie Mensgebonden Onderzoek" (CCMO).

8. CONTACT AND FURTHER INFORMATION

Further information on the BeNeFIT program, the call and the follow-up is available on the KCE (https://kce.fgov.be) and ZonMw (https://www.zonmw.nl) website. It is advised to contact the national contact person for any question regarding the call (please see national contact details below).

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9. Annexes

9.1 ANNEX I: Selection and prioritization criteria

9.1.1 Eligibility criteria

To be deemed valid and to enter the selection process, your application should:

- Be received before the deadline of **05 September 2023 14:00h (CET**, FRP phase);
- Be submitted through MijnZonMw application portal, and include all requested documents and budget using the appropriate templates and be readable;
- Be written in English;
- Include a signed letter of commitment by the Belgian or Dutch sponsor* and the national coordinating centre for the other country, using the provided templates. Letters of commitment must be signed by the legal representative of the organisation;
- The sponsor and the national coordinating centre comply with the criteria stated in section 3.1.
- Include participating centres in Belgium and the Netherlands and for Belgium, have participating centres in the Dutch and French speaking part of Belgium. In the Netherlands, one of the participating centres should be a non-academic centre. If the submission cannot comply with this eligibility criterion, justification should be provided;
- Include the name of the legal advisor from the sponsor and national coordinator institutes who has reviewed and accepted the draft consortium agreement template;
- Include a draft protocol.

** As defined in ICH-GCP*

9.1.2 Scoping criteria

- Studied interventions must potentially be reimbursable in Belgium and the Netherlands, for the Netherlands within the “basispakket” or “Wet langdurige zorg”;
- Studied interventions must already be in use in daily practice for the given indication in both Belgium and the Netherlands; outside the framework of clinical research or pilot testing;
- Submissions must be within scope of one of the two ZonMw programs ‘Efficiency Studies’ or ‘Rational Pharmacotherapy’;
- The primary aim of the trial must be of non-commercial nature. In addition, the holder of the IPR on the studied intervention or comparator to which the experiment relates is neither directly nor indirectly the sponsor of the experiment;
- The chief investigator and research team should have no important conflict of interest in regards with the possible results of the trial;
- Studies that have already been submitted to authorities, ethical committees and/or have already started recruitment are out of scope;
- Studies on prevention, screening (early detection) or tests to predict risk or response are out of scope;
- Implementation research and quality improvement projects are out of scope;
- Studies on the organisation of care are out of scope;
- Development/innovation trials are out of scope;
- Studies of medicinal products or medical devices that are not marketed in Belgium and the Netherlands are out of scope. Devices should have a CE label;
- Non-randomised trials are out of scope.

9.1.3 Evaluation criteria

Relevance

Need for Evidence	• The importance or burden of the health or care problem to those who would use the evidence generated by the proposed trial. In particular, whether the trial would likely lead to improved health and care in Belgium and the Netherlands and contribute to change in daily practice. • What the proposed trial would add to the existing body of knowledge based on a well-documented search for completed and ongoing research.
PICO (Patient, Intervention, Comparator, Outcome)	• The trial is a non-commercial trial of interventions already in use in Belgium and the Netherlands in daily practice for the studied indication. No treatment or placebo are accepted as a study intervention. • Studied interventions should be reimbursed already or be eligible for possible reimbursement in Belgium and the Netherlands if trial results show effectiveness. • Trials evaluating new interventions in development are excluded. Research into the organisation of care and implementation research are not eligible for this call. Also, trials evaluating screening, prevention or tests to predict risk or response are excluded. • The trial intervention(s) should reflect current clinical practice as close as possible. • Outcomes are patient centred and include the core outcome set, if available.
Value for money and potential Return On Investment (**ROI**) for the healthcare systems in Belgium and the Netherlands	• The costs of the trial are reasonable in relation to the likely benefit of the research to decision-makers, patients and the public. In particular, in addition to the health benefits, the results of the research could lead to net savings for the Belgian and Dutch healthcare systems or the promotion of more cost-effective interventions (ROI). • Each trial should have the potential of generating results with an immediate and important impact on the efficiency of the health care systems in Belgium and the Netherlands, without the need for an additional research. • A score will be given: 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 that 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 this will receive a low score.
Implementation	• There should be a clear implementation plan, describing how the results will be implemented and will have an impact on daily practice, e.g. via international guidelines and/or reimbursement. Ideally the project will relate

	to a guideline that is supported by professionals in the two countries.
Patient involvement	• The funding agencies strongly encourage patient involvement in research. A clear description of patient involvement needs to be included in the application. Preferably, the research question should be ranked high by patient panels. The involvement of patients in the development of the project (selection of patient-relevant study endpoints, feasibility of trial assessments) and their continued involvement through the lifecycle of the research project is required for submissions to the call. • A lay summary in English should be included.

Scientific quality

Design	• The trial 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. • The trial should have a randomised (at individual level or in clusters) and multi-centre design. • The use of centralised randomisation and e-CRFs are recommended. • Only a limited set of variables, needed for the pre-planned analyses, are to be collected. All variables collected need to be well justified.
Sponsor* (Main applicant)	• The sponsor's team has the necessary skills, procedures, facilities and experience in conducting non-commercial multicentre trials and has the ability to comply with all sponsor related obligations. • The investigators at all trial sites demonstrate an expertise in the disease and patient population that will be studied.
Patients	• At least two sites in Belgium and two sites in The Netherlands should participate in the trial.[$] Participating centres in other countries are allowed if co-financing is provided. Funding of centres outside of Belgium and the Netherlands cannot be included in the BeNeFIT budget. • The number of patients recruited in each country should be sufficiently high to justify the country specific start-up and coordination costs. • 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 the funding agencies to verify these requirements during a trial site visit.
Timelines	• The risk of recruitment delay is considered low. • The trial results at the time of publication should still be clinically relevant.
Trial budget	• The proposed costs of the research are reasonable and commensurate with the work involved.
Terms and conditions	• The terms and conditions of the proposed collaboration between the sponsor and the funding agencies, as formulated in the "Terms and

	Conditions" of the call (including data sharing, possible commercialisation, etc.), should be accepted by the applicants' research team and possible other funders. • A data management plan should be made available when the full research proposal is submitted.
Other external funding	Other funding will be allowed only if "terms and conditions" for the BeNeFIT funding are accepted by all parties.

[$] *If not possible, please justify*

9.1.4 Prioritization criteria Call Steering Committee

Prioritization and selection by the Call Steering Committee (CSC) can change the Scientific Evaluation Committee (SEC) ranking of research outlines or full research proposals, based on the following additional criteria (in no particular order):

- Potential Return On Investment (ROI);
- The evaluation by the SEC, external reviewers and the feasibility study;
- The regional spread of the participating centres, aiming for a balanced representation of Belgian and Dutch centres (and for Belgium: a good representation of Dutch and French speaking centres);
- The (inter)national spread of the main applicants. The CSC strongly aims to have at least one main applicant in each country;
- The overall budget of the call and the distribution of the budget among the two funding agencies.
- The distribution of the Dutch budget among the ZonMw programs. The contribution of ZonMw is divided among trials that fall within the scope of the ZonMw ”Efficiency Research” program and the ZonMw “Rational Pharmacotherapy” program. Each program has a maximum budget, no shift to the other program is possible;
- The overall portfolio in terms of disease areas, types of interventions and settings.

9.2 ANNEX II: Timelines BeNeFIT call

Deadlines and meetings applicants

27 October 2022		Opening call on website
8 February 2023	14:00	**Deadline** submission Research Outline
Medio May 2023		First decision letter CSC
7 June 2023		Strengthening workshop – selected applicants only
05 September 2023	14:00	**Deadline** submission Full Research Proposal
30 October 2023		Prepare rebuttal
8 September 2023		Start feasibility checks
15 December 2023		Finish feasibility reports
15 January 2024	14:00	**Deadline** submission rebuttal
May 2024		Final decision letter CSC

9.3 ANNEX III: State aid

This applies to Dutch parties only.

State aid

ZonMw will provide the grand under the Service of General Economic Interest (SGEI) Exemption Decision[1], provided the conditions have been met.

ZonMw has considered the activities described under the heading “aim of the call” to be economic activities of general interest. ZonMw will, by means of a decision, charge the consortium, for the activities described above with the administration, of a SGEI.

The BeNeFIT third call is aimed at comparative studies researching how an existing medical treatment can be used more efficiently, including in terms of costs, for example by offering personalised treatments, lower dosages or shorter treatments, or researching whether a cheaper alternative would have the same effect. In addition, treatments could be studied for groups to which manufacturers of medicinal products and devices devote little or no research, including those with rare diseases, pregnant women, children and the elderly. This refers to clinical, experimental research performed in the context of projects in which efficacy, efficiency and safety are at the centre of the treatments being researched. This always involves social questions that add to the general public interest in improving the quality, affordability and accessibility of health care in the Netherlands and Belgium – questions which the market declines to address because it has no financial interest in them. Consequently, the market forces create a negative impact on society and suppresses positive factors from which society can profit.

The SGEI consists of implementing the activities described in the project proposal. The grant can only be used for SGEI activities. Consortium undertakings that receive grants in this funding round are obligated on the grounds of Article 5(2) of the SGEI Exemption Decision to list revenue and expenditure associated with activities in the service of general economic interest separately from revenue and expenditure for other activities that do not fall within the SGEI.

Project funding will not exceed the maximum duration of the project. In line with the SGEI Exemption Decision, the maximum duration of a project is 10 years.

The grant amount applied for may not exceed the net cost of the planned project activities. The parameters for calculating the compensation for each project are included in the budget documents of ZonMw. The calculation methods included in the submitted budget are in accordance with Article 4 of the SGEI Exemption Decision. ZonMw will recover any proven overcompensation on the basis of Article 6(2) of the SGEI Exemption Decision. If the project duration exceeds 3 years, ZonMw will perform an interim check to establish whether there has been any overcompensation.

If, at the time of application, it is still unclear which parties are participating in the consortium, it is possible to add these parties to the consortium at a later stage. If a new party is added to the consortium, please notify ZonMw of this in writing. The new party will only be included in the consortium if ZonMw has approved this. All parties must individually meet all the conditions of the SGEI Exemption Decision.

If the project activities are shown not to have been carried out, or not to have been carried out in full, or if the obligations attached to the grant have not been fulfilled, ZonMw may set the grant at a lower amount and recover all or part of any advance payments made.

[1] Commission Decision of 20 December 2011 on the application of Article 106(2) of the Treaty on the Functioning of the European Union to State aid in the form of public service compensation granted to certain undertakings entrusted with the operation of services of general economic interest, 2012/21/EU, PB EU 2012 L7/3.

9.4 ANNEX IV: prioritization matrix

Prioritization matrix:

		RELEVANCE		
		high	medium	low
QUALITY	high	A	C	
	medium	B	D	
	low			

High score: mean score 4-5
Medium score: mean score: >2 - <4
Low score: mean score ≤ 2