Belgium-Netherlands Funding of International Trials

Second Call

Call text – Full Research Proposal

3-June-2021

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1. BACKGROUND

In July 2020 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 second call of the Belgium-Netherlands Funding of International Trials (BeNeFIT) program.

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 Trials 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 2017 KCE Trials and ZonMw launched the joint program 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 research institutions from both countries.

Selection of research outlines submitted to this second BeNeFIT call have taken place in March 2021. The BeNeFIT call steering committee now invites selected research teams to submit their full research proposal.

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 in 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 a 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. In Belgium, both French-speaking and Flemish centres should participate.

** As defined in ICH-GCP*

*** Co-sponsorship is possible for clinical trials within the scope of Regulation (EU) No 536/2014 once it comes into application.*

Belgium

- If the sponsor is located in Belgium, the sponsor 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 Netherlands

- If the sponsor is located in the Netherlands, the sponsor 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 subsidy will be granted if this would or could lead to the granting of unlawful state aid. If companies apply for funding within this call, ZonMw will grant subsidy within the scope of the Commission Decision on services of general economic interest (SGEI Decision, in Dutch: DAEB Vrijstellingsbesluit[β]), if the conditions are met. For an extensive explanation of state aid, as well as the SGEI Decision and its consequences for a Dutch sponsor or coordinating centre, see annex III.

A national coordinating centre must be assigned in the country where the sponsor 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.

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.

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 (with 'no treatment' or placebo being one of the possible treatment options) that are already in use in the health care system in 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 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.

[$] *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).*

[β] *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.*

Proposals will be selected based on the need for evidence in clinical practice and possible efficiency improvement and potential return on investment for the health care systems. The primary aim of the trial must be of a non-commercial nature.

Out of scope (see Annex I (9.1.2):

- 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 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 subsidy 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 4.1).

The evaluation criteria are listed in Annex I. 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 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 proposals and the final selection and award of the trials.

- **The Call Steering Committee (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 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 Scientific Evaluation Committee (SEC)** is a panel of internationally recognised scientific experts and representatives of patients, 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 BeNeFIT 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 3-step selection procedure:

1. The submission of an initial research outline (RO) outlining the key information on the research proposal (this phase was finalised March 2021);
2. Invitation to submit a full research proposal (FRP) for ROs shortlisted by the SEC and CSC;
3. Invitation to submit a revised full research proposal for FRPs selected by the SEC and CSC; revised FRPs should include a more elaborated feasibility assessment, see 4.4.4.

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 meeting 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 3.3). ROs that are out of scope will be declined without further review.

Research outlines that are eligible and in scope will be forwarded to the SEC members for evaluation. The SEC will evaluate the ROs for relevance and scientific quality, based on the criteria listed in Annex I (9.1.3). Individual SEC members will evaluate the ROs with a score between 1 and 5 for both relevance and quality. The ROs will subsequently be ranked according to the mean scores (mean score 4-5 is high, mean score >2-3,9 is medium, mean score ≤2 is low) and the prioritization matrix in Annex IV).

Further prioritization and selection of the SEC ranking order by the CSC is based on the additional criteria listed in Annex I (9.1.4) and available budget. CSC decisions are taken in consensus, meaning that ROs that go to the next round have received approval from both KCE Trials and ZonMw.

The CSC can decide, based on the additional criteria (Annex I – 9.1.4), to prioritize particular ROs in order to keep an overall portfolio that is balanced in terms of regional and budgetary spread and ZonMw programs. Meaning that highly ranked ROs (based on the scores by the SEC) may not necessarily be prioritized and selected. The number of ROs that will be invited to submit a full research proposal (FRP) will be limited. The selection will be based on the available budget and aiming for a funding success rate of at least 50% of the FRPs received.

Invitation to submit FRP

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 an 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. For the protocol, please use a protocol template (in English) as available on the website of the Dutch “Centrale Commissie Mensgebonden Onderzoek” (CCMO).

Applicants are entitled to request to the CSC to support the development of the FRP through *ad hoc* funding (€ 12.500,- including any overhead or applicable VAT). Requests will be evaluated by the CSC upon its own discretion.

To further support the applicants in the development of their FRP, a strengthening workshop will be organised on 2 June 2021. We expect the main applicant and a representative of the coordinating centre in the other country to be present.

4.4 Eligibility check and evaluation of Full Research Proposals

4.4.1 Eligibility check

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 and right to reply (rebuttal)

Each retained FRP will be sent to a minimum of 4 external expert reviewers for a written assessment on the scientific quality and the relevance for clinical practice. External reviewers are international domain experts specifically selected for each FRP. They will receive the FRP form and draft protocol after the eligibility check and will be asked to send their comments to the BeNeFIT secretariat.

All written reports of the external expert reviewers will then be sent to the main applicant. Each applicant will have the opportunity of studying the assessments and commenting on the arguments and evaluations of the external reviewers in a written rebuttal. This stage allows applicants to comment on factual errors or misunderstandings that may have been committed by the external reviewers while assessing their proposal and to reply to reviewers' comments and questions. However, issues which are not related to reviewers' comments or questions cannot be addressed and the work plan cannot be modified at this stage. Deadline for submission of the written rebuttal is **5 November 2021 14:00h (CET).**

4.4.3 Interview and evaluation by SEC

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

In addition, the applicants will be invited by the SEC for an interview, giving them the opportunity to present their proposal and reply to questions from the SEC members. The second SEC meeting with interviews of the applicants will take place on 24 November 2021.

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

The ranking will be forwarded to the CSC, who make the final decision on which proposals will be invited to submit a revised FRP, based on the additional criteria in Annex I (9.1.4) and available budget.

Applicants of selected FRPs will be invited to submit a revised FRP that takes into account specific conditions and/or recommendations by the SEC. The revised FRP should include a more detailed feasibility and recruitment plan, see 4.4.4. Additional *ad hoc* funding of € 12.500 (including any overhead or applicable VAT) will be available upon request to the CSC for selected FRPs to compensate for the required feasibility assessment.

4.4.4 Additional recruitment check

To avoid recruitment problems and a delayed publication of trial results, the CSC requests an additional recruitment check to be included in the revised FRP. 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. More detailed information will be provided to applicants that are invited to submit a revised FRP at that time.

4.4.5 Review of revised Full Research Proposals

Review of the revised FRP will consist of an evaluation of the specific conditions and/or recommendations by the SEC (see 4.4.3) and the outcome of the feasibility assessment (see 4.4.4) and subsequent scoring for relevance and scientific quality by the SEC. External expert reviewers or an

interview are not included in this stage. Scores assigned by the SEC (see 4.3) will result in a ranking of the proposals that will be forwarded to the CSC.

4.5 Funding decision

Based on the final scores for relevance and scientific quality, the CSC will take the final funding decision. Proposals will be selected for funding following the ranking order of the SEC (based on scoring), taking into account the overall budget of the call, the contributions of each country, the national spread of the main applicants, the regional spread of participating sites (for Belgium including Dutch/French speaking), the contribution for each ZonMw program ("Efficiency Research" and "Rational Pharmacotherapy") and potential return on investment.

The contribution of each country cannot exceed the amount attributed to the call by that particular country. No additional projects can be funded when one of the countries has reached its budget limit during the prioritization process. Therefore it is possible that a country will not spend its reserved budget. To maximize the funding opportunities within this call, projects that have a balanced representation in the two participating countries (and for Belgium, in the different regions) will be prioritized. 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 4.3).

5. SUBMISSION PROCEDURE

5.1 Online portal

Proposals can only be submitted using the submission portal of ZonMw called ProjectNet. **Deadline** for the submission of FRPs is **09 September 2021 14:00h.** Submissions on paper will not be accepted.

First time users have to create an account. Practical information can be found in the manual. *Please note that your institution may not be listed in the ProjectNet database yet, in which case you have to put in a request to add your institution. Processing your request may take up to 24 hours, so please do not postpone the submission process to the last moment.*

In addition to files which can be attached to the submission, some data need to be completed directly online in the submission portal. The proposal needs to be written using the Full Research Proposal form for this BeNeFIT call. To complete the form, carefully read the guidance notes included in the form. A detailed budget must be submitted using the dedicated budget tool, for which separate guidance notes are available. The completed Full Research Proposal form (pdf) and budget tool (as pdf) need to be uploaded as attachments to your online submission in ProjectNet. The Excel version of the budget tool needs to be sent to BeNeFIT@zonmw.nl.

For technical questions, you can contact the ZonMw servicedesk via ProjectNet@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 proposal budgets. Therefore, the budget of the proposal needs to be submitted using the specific budget tool for this call.

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. Therefore, a balanced number of recruited patients in the two countries is encouraged and proposals with a balanced representation of Belgian and Dutch centres (and for Belgium, a good representation of Dutch and French speaking centres) will be prioritized. ZonMw will

pay all costs in respect of a specific trial that were incurred in The Netherlands. KCE shall pay all costs in respect of a specific trial that were incurred in Belgium.

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% 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 organised with the funding agency (ZonMw or KCE) of the country of the sponsor.

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 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 Second 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 Second 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 shall reflect said Terms and Conditions Second 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 Full Research Proposal (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 for 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. Candidates will need to submit a draft consortium agreement (approved by the partners but not yet signed) when submitting their revised full research proposal. The consortium agreement must follow the provided template. It is required for the full research proposal phase to have the IP/contract specialist from both main applicant and national coordinator review the draft consortium agreement template. It is advised, but not required, to already submit an unsigned draft consortium agreement when submitting the full research proposal. 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 included in the draft, or attached as a separate document in the application. The Funding Agencies reserve the right to assess this draft for compliance with the European law on state aid and Terms and Conditions Second Benefit Call.

Co-financing

Co-financing is possible, but any co-financer of the research will need to submit a signed letter of commitment. Candidates will need to submit a draft agreement with the co-financer (approved by the parties but not yet signed) when submitting their revised full research proposal. The Funding Agencies reserve the right to assess this draft for compliance with the European law on state aid and Terms and Conditions Second 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 full research proposal (not the research outline) 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 Intellectual Property Rights (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:

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;
c. 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 programmes 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 Second 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 Second Benefit Call.

7. LINKS & DOWNLOADS

- ZonMw ProjectNet portal
- ProjectNet short user manual (PDF)
- Application form Full Research Proposal (Word)
- 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 Second BeNeFIT Call (PDF)
- Consortium agreement template (Word)

8. CONTACT AND FURTHER INFORMATION

Further information on the BeNeFIT Project, 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).

ZonMw (call secretariat)
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kce_trials@kce.fgov.be

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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 14:00 h on 09 September 2021;
- Be submitted through the ZonMw ProjectNet portal, using the appropriate form and be readable;
- Be written in English;
- Include the name of the legal advisor from 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 are potentially reimbursable in Belgium and the Netherlands, for the Netherlands within the "basispakket";
- Studied interventions are already in use in daily practice in both Belgium and the Netherlands;
- Within scope of one of the two ZonMw programs 'Efficiency Studies' or 'Rational Pharmacotherapy';
- 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;

9.1.3 Development/innovation trials are out of scope 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 given indication. • 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 early development would be excluded. Research into the organisation of care and implementation research are not eligible for the 2020 international 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 (return on investment). • 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, preferably 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 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. • A randomised, multicentre design is highly preferred. • 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 in 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 consortium[$]. • 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 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. • 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 SEC ranking of research outlines or full research proposals, based on the following additional criteria:

- Potential return on investment (ROI);
- 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 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 participating funders. More information on how the budget will be distributed between the two funders can be found in 5.2;
- The distribution of the Dutch budget among the ZonMw programs. The contribution of ZonMw must be evenly spent to trials that fall within the scope of the ZonMw ”Efficiency Research” program and the ZonMw “Rational Pharmacotherapy” program. (A maximum of 55% of the Dutch budget can go to one of the programs).

More precisely, the CSC can decide in consensus not to shortlist one of the best ranked ROs/FRPs (based on SEC scores) but give priority to lower ranked ROs based on the additional criteria, in order to keep an overall portfolio that is balanced in terms of regional and budgetary spread and ZonMw programs.

9.2 ANNEX II: Timelines BeNeFIT call

Deadlines and meetings applicants

16 October 2020		Opening call on website
14 January 2021	14:00	**Deadline** submission Research Outline
15 February 2021		Decision eligibility
7 May 2021		First decision letter CSC
2 June 2021		Strengthening workshop – selected applicants only
09 September 2021	14:00	**Deadline** submission Full Research Proposal
15 October 2021		Prepare rebuttal
05 November 2021	14:00	**Deadline** submission rebuttal
24 November 2021		Meeting SEC to review FRPs + interview with applicants
23 December 2021		Second decision letter CSC
21 April 2022	14:00	**Deadline** submission revised Full Research Proposal
30 June 2022		Final decision letter CSC

9.3 Annex III

This applies to Dutch parties only.

State aid

ZonMw will grant the subsidy under the SGEI Decision[1] if companies participating in this call apply for a subsidy and meet the conditions in that respect. (Decision exempting services of general economic interest).

ZonMw has considered the activities described under the heading “aim of the call” to be economic activities of general interest.

The BeNeFIT 2nd 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.

Prior to granting the subsidy, ZonMw will issue a decision assigning responsibility for the operation of a Service of General Economic Interest (SGEI) to the company in question for the performance of the activities described above.

The SGEI will consist of performing the activities described in the project proposal. The subsidy can only be used for the activities that fall within the scope of the SGEI. Pursuant to Article 5(2) of the SGEI Decision, companies that receive a subsidy are obliged to ensure that the costs and revenues related to SGEI activities are kept separately in their accounts from the costs and revenues of activities that do not fall under the SGEI.

If the term of the project exceeds three years, ZonMw will perform an interim audit to ascertain whether any overcompensation has occurred.

If subsidies are granted, ZonMw will grant the subsidy to the grant applicant. If the grant applicant is a company, ZonMw will grant the subsidy under the SGEI Decision. If the applicant chooses to have third parties perform project activities, the applicant and the third party will need to enter into a market-based service agreement in order to comply with European State Aid regulations. If applicable, the applicant must comply with the rules governing tenders. The conditions of the service agreement will need to be such that the applicant will be able to meet the obligations of the grant terms and conditions such as (free) accessibility for further research, education and application, including an up- front transfer of any results generated by a third party to the applicant. ZonMw reserves the right to assess this service agreement for compliance with the European law on state aid and Terms and Conditions Second Benefit Call. In addition, the applicant must provide clarification in the application and the budget regarding the costs to be incurred (including VAT).

[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:

		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