Federal Ministry of Education and Research

Call for proposals for preclinical confirmatory studies and systematic reviews

22 June 2022

Translation (Extract)

Objective and Purpose of Funding

New therapies and better and safer drugs are needed to provide people with health care. To this end, promising therapeutic approaches and drug candidates must be identified in preclinical studies and then validated. In order to be as reliable as possible in the subsequent clinical development steps, the preclinical results should be predictive and replicable as well as backed by appropriate quality standards and validation processes. The discussions about the replicability of research results indicate that there is potential for improvement in this area[1]. Confirmatory studies[2] which follow high quality standards and test the reliability and robustness of the exploratory results can contribute to increasing the validity of health research. They thus serve as a reliable basis for further development along the value chain. At the same time, a systematic analysis of preclinical research results in the form of reviews (systematic reviews) can be helpful to get an overview of the current scientific evidence, to identify gaps, to avoid unnecessary duplication of experiments and to lay a sound basis for research projects.

Objective of Funding

The aim of this call for proposals is to support the methods and phases of preclinical research in Germany which contribute to increasing the validity, robustness and reliability of scientific preclinical research results and thus improve their translation towards application. In addition, the call shall promote a systematic evaluation of the preclinical research results in the literature, the further development of quality-assured procedures, and the publication of Null- or negative results in order to contribute to a more reliable basis for the development of therapies.

The goal of the funding program is achieved if i) clinically relevant results from the previous preclinical research are validated by confirmatory studies, thus enabling a decision to be made as to whether a continuation in the direction of clinical testing makes sense; ii) the results available in the literature on a specific research question have been systematically and transparently described and/or quantitatively evaluated through systematic reviews, so that reliable, knowledge-based conclusions can be drawn for further preclinical or clinical studies.

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[1]DFG statement: Replicability of research results, April 2017. https://www.dfg.de/download/pdf/dfg_im_profil/geschaeftsstelle/publikationen/stellungnahmen_papiere/2017/170425_stellungnahme_replizierbarkeit_forschungsergebnisse_de.pdf (last accessed on June 13, 2022).

[2]Confirmatory studies aim to empirically corroborate results from previous exploratory studies. They serve to test a hypothesis.

Purpose

Investigator-initiated, preclinical, confirmatory studies, which are implemented as cross-laboratory joint projects, will be funded within module 1. These studies should enable a decision whether the results can be transferred to further preclinical development and then to early clinical studies in a next step. In addition, systematic reviews on preclinical research topics can be funded within module 2. In both modules, the questions and research results should have a high relevance for medical care in Germany.

This call is implemented in accordance with the Health Research Framework Program.The major goal of this funding scheme is to improve translation in health research. With this call, the Federal Ministry of Education and Research (BMBF) promotes building bridges between biomedical laboratory research and preclinical or clinical development. The present call is based on a call from 2018 to promote quality in health research.

Scope of Funding

The call for proposals is divided into the following modules:

Module 1: Confirmatory, preclinical studies

Funding shall be provided for investigator-initiated, prospective, controlled, preclinical studies to prove the efficacy of a clinically relevant therapeutic approach. With these confirmatory studies, carried out in a multi-laboratory approach (multi-center), the findings previously obtained in exploratory studies are to be validated. It should be checked whether the results are suitable for subsequent further preclinical development and to be transferred into clinical studies or whether further exploratory research is necessary.

Prerequisites for conducting a multi-center, confirmatory study:

Previous exploratory studies should provide the proof of concept that an active ingredient or a therapeutic method affects the target structures in the desired manner. The quality of the exploratory study results and other preparatory work must justify to conduct a confirmatory study. To substantiate the central hypothesis, results from triangulation experiments should already be available (e.g. proof of bioavailability). The requirements (minimum criteria) that should be met in the preparatory work to justify the start of a confirmatory study are explained in further detail in the guidelines for grant applicants (see below). In order to have a good basis for planning a confirmatory study, it can be helpful to have previously conducted a validation study in one laboratory[3].

The following applies to a multi-center, confirmatory study:

Each study must have a confirmatory objective with a carefully planned study design, appropriate methods to reduce bias, as well as sample size calculation and statistical analysis. For this purpose, appropriate biostatistical expertise must be integrated in the project. As a rule, one central hypothesis resulting from previous exploratory studies is to be validated. The confirmatory study should not be an identical replication of the previous study.

[3] Replication of the exploratory results by the laboratory in which the exploratory studies were carried out (within-lab replication) in order to increase the reliability of the exploratory results, e.g. by a higher sample size, and to develop the parameters for the multi-center confirmatory study.

Central aspects and methods must remain constant; meaningful, justified deviations aiming to strengthen validity are possible (for further details see the guideline for grant applications).

To investigate the generalizability of the results (external validity), the study must generally be divided between at least two and max. three laboratories (multi-center study). This usually includes the initiating laboratory, where the exploratory study took place, as well as one or two other external partner laboratories. Additional experiments can take place in the individual laboratories, but their extent should not exceed 20% of the scope of the overall study.

The validation of a promising therapeutic approach in a confirmatory study must be carried out in disease models that are relevant to the respective human diseases and allow a prediction of the efficacy of the substance or the procedure. Adequate quality assurance measures must be taken. The data analysis and monitoring should take place independently of the execution of the study.

The BMBF supports the goal of reducing or, where possible, avoiding the use of animal models in medical research. Within the framework of this call for proposals, projects that use appropriate, scientifically accepted, alternative methods can also be funded. Applicants are expected to observe and comply with the legal requirements and relevant regulations.

In order to guarantee an efficient transfer of the preclinical results into application, it must be ensured that partners with proven expertise in the development and exploitation of new therapeutical methods are involved in the research network. The prospects for clinical applicability as well as for commercialization of the therapeutic approach must exist.

Module 2: Systematic Reviews

Funding is provided for systematic reviews and meta-analyses of preclinical studies according to international standards to analyze the evidence base of preclinical research results in a specific disease area.

Experience in conducting systematic reviews and meta-analyses, if possible in the field of preclinical research, must be available. Alternatively, appropriate experts must be involved in planning and implementation.

Grant Recipients

State and state-recognized universities and non-university research institutions are eligible to apply.

Special Funding Requirements

Previous achievements

Applicants must provide proof for relevant preliminary work. This applies in particular to preclinical research methodology (including study design for preclinical studies and systematic reviews and meta-analyses). The following applies to Module 1: The planned experimental methods must already be successfully established when the proposal is

submitted, including at the partner laboratories. Relevant preliminary work on the disease, and preliminary work on which the hypothesis to be validated is based on, must be shown. The relevance of the disease models to be used for the confirmatory studies must be sufficiently proven.

For both modules, the expertise and capacities required for the respective research goals must have been adequately integrated into the project. The infrastructure required to carry out the project is a prerequisite.

Collaborations

All scientific partners and expertise required for the progress of the project must be included in the consortium. A coordinator is to be nominated by the partners of the consortium. The consortium partners regulate their collaboration in a written collaboration agreement.

In order to advance the establishment of the above-mentioned research components, it is planned that an independent accompanying project supports the funded projects with consulting and network building and performs accompanying scientific research. For this purpose, a scientific accompanying project, which builds on the preliminary work and results of the accompanying project from the first funding round, will continue to be provided.

All grant recipients must actively cooperate with the accompanying project and the related activities.

Scientific standards

Applicants must comply with national and international standards for quality assurance in preclinical research. For Module 1 the current version of the GCCP[4], PREPARE[5] and the ARRIVE[6] guidelines must be taken into account. For systematic reviews and meta-analyses (module 2), the tools and information from "CAMARADES"[7], " SyRF" [8] and the PRISMA Reporting Guidelines[9] should be taken into account.

Quality of the methods used

A funding prerequisite is a high quality of the methodology of the project. When planning the project, the national and international state of research must be systematically surveyed and adequately taken into account. The continuous integration of methodological expertise into the project must be ensured. In the confirmatory studies (module 1), biostatistical expertise (if possible with specific experience in preclinical study design) must be involved in the planning, the analysis, and to a reasonable extent in the implementation of the project. With the submission of the project outline, the correctness of the statistical planning and analysis procedure of the study must be verified by the signature of the biostatistician.

Consideration of aspects of biological sex

[4] GCCP: Good Cell Culture Practice, z. B. https://www.altex.org/index.php/altex/article/view/2376/2327
[5] PREPARE: guidelines for planning animal research and testing: https://journals.sagepub.com/doi/pdf/10.1177/0023677217724823
[6] ARRIVE (Animal Research: Reporting of In Vivo Experiments)-Guidelines: https://arriveguidelines.org/
[7] CAMARADES: https://www.camarades.de/
[8] SyRF: https:// syrf.org.uk /
[9]PRISMA Guideline: http:// prisma-statement.org / ; https://pubmed.ncbi.nlm.nih.gov/33789819/ _ _

The relevance of the biological sex for the research question of the project must be checked. The assessment and how the biological sex will be addressed methodologically, must be described in the proposal.

Accessibility, interoperability and long-term security of research data and results

Access to scientific findings and data is an essential basis for research, development and innovation. Long-term and sustainable back-up and provision of research data contributes to the comprehension, reproducibility and quality of research, as well as to their use for future research questions and findings. The establishment of parallel structures for data access and data storage should be avoided.

FAIR principles (findable, accessible, interoperable and reusable, see https://www.go-fair.org/fair-principles/) for data management must be complied to. Further information on handling research data can be found in the following checklist: https://www.dfg.de/foerderung/basic-conditions/research-data/index.html .

Accordingly, the following conditions apply:

- The protocols for confirmatory, preclinical studies as well as for systematic reviews and meta-analyses should be registered and/or published in suitable registers before starting the project work;
- data management plans should be developed and provided;
- research results developed within the framework of this call must be published independently of the outcome, i.e. also in case of negative (NULL-) results (e.g. non-confirmation of a hypothesis);
- results should be published in open access journals;
- original data of publications should be made available using current international standards (e.g. HL7 FHIR) for exchange and subsequent (digital) use (the rights of third parties, particularly data protection and copyright issues must be respected);
- data access and data accessibility rules for third parties must be described in the proposal and, in case of funding, published.

Possibilities of exploitation and use

The expected results must provide definite knowledge gain for future therapeutical developments. Confirmatory studies must therefore be designed in such a way that after running the project, the results can be described with the necessary and sufficient parameters, to allow a decision on the feasibility of further development steps in the value chain. The planned further exploitation, the transfer of the results into further development steps and the strategies for sustainable implementation must already be described in the proposal.

For confirmatory studies (module 1), applicants must have checked and described the patent situation for the corresponding medical treatment or product in the proposal, and protect worthwhile results. Applicants have to describe whether they own property rights and whether property rights exist that may prevent further developments. The grantee must be free to use the project results for commercial or research purposes (freedom to operate). In

addition, applicants must mention whether they will aim for further property rights. Applicants may have already contacted a company or plan to do so during the course of the project to take further steps towards clinical development (follow-up studies).

Type and scope, amount of the grant

Funding will be provided as a non-refundable grant.

Applicants outside the commercial sector are eligible for funding for project-related additional expenses such as personnel, consumables, and travel expenses as well as, in justified exceptional cases, project-related investments that are not attributable to the applicant's institutional infrastructure and supply.

Confirmatory studies (module 1) can usually be funded for a period of two to three years, systematic reviews (module 2) for a period of up to two years.

Part of the eligible expenses/costs are also the following aspects:

a) For the execution of the research projects, e.g.

- Preparation of the detailed study protocol;
- Registration of the study or systematic review;
- Monitoring or consulting on quality assurance; the introduction of quality assurance measures, e.g. for the validation of reagents, biologicals, cell lines and model systems; for electronic laboratory books; the structured documentation and storage of data; travel expenses for meetings and workshops for the collaboration with the accompanying scientific project;
- Fees for Open Access publications of the project results during the duration of the project;
- Replacement staff for clinical scientists to be released full of part time from their routine tasks in clinical care and for whom a replacement must be hired.

b) Coordination and services, e.g.

- Processing of project-specific research data during the funding period for subsequent use by other scientists (open data);
- Infrastructure and costs for personnel during the funding period for the controlled release of the data and their transfer to existing data infrastructures.

The expenses/costs required to obtain, validate and maintain patents and other commercial property rights during the project lifetime are eligible for funding.

Collaborations with thematically related projects in other European and non-European countries is possible, whereby the international partner must have its own national funding for its project share. Additional expenses for e.g. scientific communication, workshops and project meetings stays of young scientists (doctoral students, postdocs) of the network at

external research institutions and clinics as well as the invitation of guest scientists are generally eligible for funding if thereby synergistic effects can be expected.

If the collaboration with a foreign group seems necessary for the execution of an essential sub-project, expenses/costs for personnel and consumables are eligible for funding using a "subcontract". The prevalent need and the scientific added value must be justified.

Procedure

Selection of project outlines

Submitted proposals will be evaluated by an independent review panel along the following criteria:

Module 1:

- Compliance with the call objectives and funding requirements;
- clinical relevance of the research question;
- translational relevance and chances of success of the project;
- scientific and methodological quality of the available evidence from the preliminary work (including from an exploratory study);
- scientific excellence and methodological quality of the confirmatory, preclinical study;
- Competence and experience of the applicant or the consortium;
- Quality and appropriateness of the management structures and procedures;
- Feasibility of the project: quality and effectiveness of the work plan, feasibility of the time plan;
- Strategy and quality of the proposed measures to exploit and disseminate the project results;
- Appropriate financial planning.

Module 2:

- Compliance with call objectives and funding requirements;
- clinical relevance of the research question;
- translational relevance and chances of success of the project;
- scientific excellence and methodological quality of the systematic review or meta-analysis;
- Competence and experience of the applicant or the consortium;
- Quality and effectiveness of the work plan;
- Strategy and quality of the proposed measures to exploit and disseminate the project results;
- Appropriate financial planning.

The full text of this call is available in German at:

https://www.gesundheitsforschung-bmbf.de/de/14868.php