

German Clinical Trials Programme Information for Reviewers

I. General information for the Reviewers

As a rule, every proposal submitted is evaluated by at least two, usually three independent reviewers. Taking into consideration these written reviews, the review board makes an award recommendation. For proposals sent to the DFG, the complete documentation is then sent to the Main Grants' Committee, which takes the final funding decision. For proposals sent to the BMBF, the Ministry itself instead takes the final decision of award.

All reviewers participating in the process will be informed of the final decision.

The funding organisations make an effort to identify reviewers who have extensive knowledge in the field without being linked to the applicants through co-operation, direct competition or in other ways. However, nobody is perfect. Therefore:

Please examine whether circumstances exist that could be interpreted as your having a conflict of interest. If for whatever reason you do not feel able to carry out the review please return the proposal as quickly as possible. In this case we would be grateful if you could assist us by suggesting other possible reviewers. In case of any questions about the proposal, please contact the funding organisations exclusively (not, please, the applicant or any third person).

When preparing the review please consider that the head office may forward your comments on the proposal to the applicant in an anonymous form.

II. The Clinical Trials Programme

The German Research Foundation (DFG) and the German Federal Ministry of Education and Research (BMBF) launched a joint programme to support clinical trials in 2003. Each organisation originally set aside a total of €5 million per year. Due to the success of the first yearly round of the programme the DFG and the BMBF increased their annual allocations in 2008 to €15 million per organisation (€30 million total per call).

The programme's objective is to significantly improve investigator initiated trials in Germany and to increase the ability of German university clinics to design and conduct internationally competitive trials. The DFG and the BMBF expect that, by coordinating their efforts, they will contribute to sustainable improvements in this field. The funding programme is focussed on scientifically excellent confirmatory multi-centre interventional trials. Funding of systematic reviews is possible, though to a much lesser extent.

The DFG will primarily fund

- Interventional, confirmatory prospective controlled clinical trials on non-pharmacological therapeutic procedures
- interventional, confirmatory prognostic trials
- interventional, confirmatory controlled trials on secondary prevention
- interventional and non-interventional, confirmatory prospective diagnostic trials in phases II-III (according to Sackett)

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The Ministry's Programme Management Agency for this programme is: Projektträger Gesundheitsforschung für das BMBF, Heinrich-Konen-Str. 1, D-53227 Bonn, Tel. +49 228 3821-0; Fax: +49 228 3821-229; Internet: www.PT-DLR.de

The BMBF will fund

- prospective controlled interventional confirmatory trials on pharmacological therapies

Gender and age-group specific aspects should be taken into account in all trials. Trials will not be considered for funding if companies have immediate commercial interests in the results. Applicants must have completed appropriate preliminary work relevant to the clinical trial. All trials funded within this programme must comply with international standards (Good Clinical Practice (ICH-GCP), Declaration of Helsinki, CONSORT Statement).

Proposals with an initial funding duration of three years may be submitted, extending applications after three years are possible. The BMBF may consider funding longer running trials directly. Only expenditures incurred by the study itself can be funded: Staff, consumables, monitoring (audits may be initiated by the funding organisations), travel and expense allowances for participating advisory boards, travel allowances, insurance coverage, registrations fees, specific tests and analyses, expenses derived from collaboration with trial centres abroad.

Applications are considered through a two-stage assessment procedure: outline and full proposal stages.

III. Information on the Reviewing Process

1. Outline proposals

First outline proposals must be submitted. They have to be prepared according to a template provided by the funding organisations and be signed by the principal investigator and the responsible biostatistician. Outline proposals not in accordance with these rules will not be considered.

All outline proposals, regardless to which funding organisation they were submitted, will be reviewed by the "Clinical Trials"-Board, an independent international review panel.

Board members / reviewers receive a subset of the outlines submitted. In assessing the outline proposal, the following questions should be addressed and scored:

Clinical evaluation

Starting hypotheses

- How clearly is the existing evidence described and discussed?
- How convincingly does the evidence presented support the trial rationale?
- How justifiable is a confirmatory trial (phase III or a late phase II trial) at this stage?
- How well-founded is the estimated effect size?
- In a diagnostic trial: is the gold standard well chosen?
- In a diagnostic/prognostic trial: is there a clear concept for clinical or epidemiological action/ further steps in research?

Innovation and Relevance of the trial

- How significant is the trial in terms of its potential impact of relieving the burden of disease and/or improving human health?
- How novel is the addressed question?

Design aspects

- How suitable are the control(s) / comparator(s)?
- How clinically relevant are the clinical outcome measures?

Qualification of applicant(s)/trial management

- How qualified is the team of investigators?

Biostatistical evaluation

Hypothesis

- Is the hypothesis of this study precise enough?
- Is the primary hypothesis in line with the design of the study?
- In an active controlled trial: is the assumption about the efficacy of the comparator substantiated?
- In a diagnostic trial: Do the measures (like sens, spec, PPV and NPV) and their relative importance match to the intention of the research question?

- In a prognostic trial: is the target and study population adequate (internal and external validity)?
Are the clinical or epidemiological consequences of prognosis adequately discussed?

Design aspects

Is the study design adequate to answer the question posed?

Randomisation

How appropriate are the proposed arrangements for allocating participants to trial groups?

Sample-size calculation

- How convincing are the assumptions (assumed differences etc.) underlying the sample size calculations?
- Are references given to substantiate these assumptions?

Analysis

- Is the primary analysis population specified and appropriate?
- How adequate is the proposed strategy of statistical analysis

Each outline proposal is assessed by two clinical as well as one statistical reviewer, giving an overall score. Constructive and concise feedback to applicants is also requested. Fundamental and irreparable flaws in concept and design should be reflected in lower scores. The assessment forms should be submitted prior to the board meeting as the overall score serves to rank the outlines to facilitate discussion during the board meeting.

As the aim of the board meeting is to identify the very best trials to be taken to the full proposal stage a rigorous scoring is expected. All outlines are considered in full competition to each other, regardless of discipline. Thus, board members / reviewers are asked to screen for those projects that are of high scientific interest and for which a high clinical impact can be assumed. All other projects should be eliminated.

2. Full proposals

If evaluated positively, applicants will be invited to submit a detailed full proposal according to a template provided. Full Proposals are considered by external referees and subsequently by the „Clinical Trials“-Board in full competition to each other, regardless of discipline.

2.1 External Referees

Each proposal is submitted to three independent external referees (to clinical experts in the specific field, usually not board members, as well as one biostatistician). The review in writing will suitably be limited to 1-2 pages, as appropriate for the complexity of the proposal. A **clear recommendation** as to whether the project should be funded or not should be provided. Funding ratios vary widely on a scale reaching from two in five to one (or less) in ten. However, in the first instance the funding recommendation should always be based on whether reviewers think the research is worth being done. The criteria that referees are asked to consider when assessing the full proposal can be found below (cf. IV.)

2.2 „Clinical Trials“-Board

Board members will discuss the applications taking into consideration the written statements of the external referees. Each application is presented by two board members as ‘rapporteurs’. The board discussion will identify the most excellent and most important trials by asking:

- How important are the questions, or gaps in knowledge, that are being addressed?
- Is the clinical impact high?
- Will the trial make a powerful difference in patient care in the immediate future?
- Is the trial internationally competitive?
- Is the trial feasible?

IV. Criteria for the Assessment of Clinical Trials

1. Clinical evaluation

Starting hypotheses

Is the general evidence in the proposal

- clearly established by providing and discussing published or own data,
- convincingly supporting the trial rationale?

Is the effect size of the experimental intervention

- supported by providing and critically evaluating published or own data,
- of considerable clinical relevance for the patient?

In a diagnostic/prognostic trial:

- is the gold standard well chosen?
- is there a clear concept for clinical or epidemiological action/ further steps in research?

Significance of the topic / ethical considerations

- How novel is the addressed question?
- How significant is the trial in terms of its potential impact of relieving the burden of disease and/or improving human health?
- Is the trial ethically acceptable?

Design aspects

- How appropriate are control(s) / comparator(s), inclusion / exclusion criteria (generalisability and representativeness), outcome measures, methods against bias, sample size / power calculations / statistical analyses?
- How feasible are recruitment rates?

Qualification of applicant(s)/trial management

- Does the proposed team of investigators possess the necessary range of expertise and documented experience to successfully carry out the proposed trial?
- Is the trial co-ordination convincing? Are advisory bodies necessary and adequately defined?

Commercial exploitation

- Could a company have a substantial economic benefit from the potential trial results?

Financial Details

- Are the resources requested fully justified in terms of the research proposed?

2. Biostatistical evaluation

Study design

- Is the study design adequate to answer the proposed question?

Hypothesis

- Is the hypothesis of this study precise enough?
- Is the primary hypothesis in line with the design of the study?
- In an active controlled trial: is the assumption about the efficacy of the comparator substantiated?
- In a diagnostic trial: Do the measures (like sens, spec, PPV and NPV) and their relative importance match to the intention of the research question?
- In a prognostic trial: is the target and study population adequate (internal and external validity)? Are the clinical or epidemiological consequences of prognosis adequately discussed?

Randomisation

- Is randomisation stratified for important prognostic factors? Is the number of strata acceptable?

Sample-size calculation

- Are the references given, from where the assumptions underlying the sample-size calculation can be verified?
- Is there a discussion about the impact of non-compliance and missing values on the sample-size?

Analysis

- Is the primary analysis population specified and appropriate?
- How adequate is the proposed strategy of statistical analysis? Is the randomisation scheme reflected in the analysis?

- If a substantial amount of missing values can be expected: is there a discussion, which analysis strategy is conservative?

Funding recommendation / comments

Please give a clear funding recommendation: fund (high, medium, low priority) or reject. Also give comments for the applicants if you feel that this might be helpful.

V. Confidentiality

All proposals submitted, the correspondence forwarded to you, the reviews and the identity of the reviewers and members of Review Boards participating in the evaluation must be treated confidentially. They must not be revealed to third parties. Therefore, the responsibilities of a reviewer may only be undertaken personally and may not be delegated to third parties. The scientific content of the proposal may not be exploited for personal or other scientific purposes. Furthermore, we ask that you do not identify yourself as a reviewer to the applicant or to any third party.

VI. Conflict of Interest

In each stage of the proposal process the head office examines whether or not a conflict of interest may exist. A conflict of interest is given if you are directly affected by the subject matter of the funding project or another reason exists that is suitable to raise doubts about the impartiality of your specialist evaluations. Before submitting your written review or before participating in a group of reviewers, please inform us whether circumstances exist that could be interpreted as a conflict of interest. Please inform us of any possible reservations so that the head office and you together can determine whether your participation in a particular review process is opportune.

The mere appearance of a conflict of interest means that you will not be able to participate in this particular review process. You may not submit an evaluation in the written process. As a member of a group of reviewers, we ask that you leave the conference room before the oral consultations about the proposal in question begin. During a final review of several proposals, you will abstain from voting on the proposal for which it appears that you may have a conflict of interest.¹

VII. Obligation to Follow Rules of Good Scientific Practice

The rules of good scientific practice also apply to reviewers. A violation of these rules can exist if in a scientific context false information is provided intentionally or with gross negligence, the intellectual property of others is infringed upon or the research activity of others is impaired in some other manner. Violations may also occur in cases of non-compliance with sections V and VI above. The circumstances of the individual case are decisive.

¹ Such circumstances may include the following:

- Personal relationships, personal ties or conflicts;
- Close scientific collaboration, e.g., implementation of joint projects or joint publications within the past 3 years;
- Direct scientific competition with personal projects or plans;
- Close proximity, e.g., member of the same scientific institution or impending change of the reviewer to the institution of the applicant or vice versa;
- Teacher/student relationship, unless independent scientific activity of more than 10 years exists;
- Dependent relationship in employment during the past 3 years;
- Participation in ongoing or just previously concluded professorial appointment proceedings;
- Current or prior activity in advisory bodies of the applicant's institution, e.g., scientific advisory boards;
- Participation in mutual review processes, also outside of the DFG process, at least within the past 12 months;
- Personal economic interests in the funding decision;
- Competitive relationship or common economic interests, e.g., common business management.

Depending on the type and severity of the determined misconduct, the DFG may impose one or more sanctions. These may range from a written reprimand to the loss of eligibility to submit proposals to the DFG for one to eight years or the exclusion from serving as a reviewer or in statutory bodies of the DFG as well as the disqualification of the active and passive right to vote for statutory bodies of the DFG.