



Leitfaden für die Antragstellung „Klinische Studien“

Einreichen von vollständigen Anträgen

Anträge sind entsprechend den Vorgaben dieses Leitfadens zu gliedern. Anträge, die den Vorgaben des Leitfadens nicht entsprechen, können nicht berücksichtigt werden.

Neben diesem Leitfaden gelten weiterhin die entsprechenden Merkblätter und Richtlinien des BMBF¹, soweit in diesem Leitfaden nicht ausdrücklich andere Regelungen getroffen sind.

Hinweise und Muster zum Leitfaden sowie weiterführende Links finden Sie auf den Internetseiten des BMBF. Die dort veröffentlichten Anforderungen/Informationen werden regelmäßig aktualisiert. Eine Durchsicht vor dem Verfassen des Antrags wird dringend empfohlen.

¹ BMBF/ Projektträger: Richtlinien für die Zuwendungsanträge auf Ausgabenbasis (AZA) des BMBF (<http://www.kp.dlr.de/profi/easy/bmbf/pdf/0027.pdf>). Für die wissenschaftliche Begutachtung ist in jedem Fall zunächst ein Antrag nach dem vorliegenden Leitfaden einzureichen.

Application for the Funding of a Clinical Trial (12 pages max.)

FUNDING MEASURE: Please indicate the funding measure you apply for

Please prepare your application in English **not exceeding 12 sides for the headings 1. to 8.**, including a maximum of 1 page of references (DIN A4, at least 10 point Arial). Structure your application using the headings listed below. Make an entry under every heading. For the information of the reviewers, refer to the respective chapter in the trial protocol for further details if necessary. Signatures of principal / coordinating investigator and responsible biostatistician are mandatory. **Submit application, appendix, and the trial protocol according to GCP.**

Note: Applications that fail to comply with these requirements will be considered incomplete and will be rejected without peer review.

1. STUDY SYNOPSIS

APPLICANT / COORDINATING INVESTIGATOR	Name, address, telephone, fax, e-mail In case of multiple applicants the principal investigator / coordinating investigator ² of the trial who will assume responsibility for conducting the clinical trial, should be listed first. <ul style="list-style-type: none"> • First name, last name, academic title • Employment status • Date of birth, nationality • Institution and department (complete name) • Postal address • Telephone • Fax • E-mail address • Private address and telephone
TITLE OF STUDY	<i>The title of the study (not exceeding 140 characters) should be as precise as possible. In case of funding this title shall be quoted in the annual reports of the funding organisations. Acronym is optional.</i>
CONDITION/TOPIC	<i>The medical condition being studied (e.g. Parkinson, depression, asthma).</i>
OBJECTIVE(S)	<i>Which principal research questions are to be addressed? Specify clearly the primary hypotheses of the trial that determine sample size calculation.</i>
INTERVENTION (S)	<i>Description of the experimental and the control treatments or interventions as well as dose and mode of application. For diagnostic tests or procedures the experimental test and the gold-standard or reference procedure should be described.</i> <u>Experimental intervention:</u> <u>Control intervention:</u> <u>Duration of intervention per patient/subject:</u> <u>Experimental and/or control off label or on label in Germany:</u>

² "Investigator" as defined in the harmonised "Guideline for Good Clinical Practice" of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH GCP) (<http://www.emea.eu.int>). This definition should be used accordingly for non-drug trials/ studies: (1.34 Investigator) "A person responsible for the conduct of a clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator." (1.19 Coordinating investigator) "An investigator assigned the responsibility for the coordination of investigators at different centres participating in a multicenter trial."

	<i>(only applicable in drug trials)</i>
KEY INCLUSION AND EXCLUSION CRITERIA	<u>Key inclusion criteria:</u> <u>Key exclusion criteria:</u>
OUTCOME(S)	<u>Primary efficacy endpoint:</u> <u>Key secondary endpoint(s):</u> <u>Assessment of safety:</u>
STUDY TYPE	<i>e.g. randomized / non-randomized, type of masking (single, double, observer blind), type of controls (active / placebo), parallel group / cross-over</i>
STATISTICAL ANALYSIS	<u>Efficacy:</u> <u>Description of the primary analysis and population</u> <u>Safety:</u> <u>Secondary endpoints:</u>
SAMPLE SIZE	<u>To be assessed for eligibility (n = ...)</u> <u>To be allocated to trial (n = ...)</u> <u>To be analysed (n = ...)</u>
TRIAL DURATION	<u>First patient/subject in to last patient/subject out:</u> <u>Duration of the entire trial:</u>
PARTICIPATING CENTERS	<i>How many centres will be involved?</i> <i>How many centres have signed an agreement to participate? To be detailed in the trial protocol</i>
PREVIOUS DFG / BMBF PROJECT NUMBER	<i>If applicable, the DFG/BMBF code number of the latest application or of any previous application(s) for project-funding concerning this study.</i>

1.1 SUMMARY

Give a summary of the main aspects of the project; it should not exceed 15 lines (max1600 characters). The project summary serves two main goals: It will inform the multidisciplinary committees, which make the final decision on your grant, of the principal aspects e.g. goals, design, subjects, expected outcome of your project.

If your project is funded the summary will be published on the internet through an electronic information system. It should therefore be concise as well as comprehensible to a lay public. Electronic search will be helped if you avoid abbreviations and include suitable key words.

1.2 KEY WORDS

1.3 FREQUENCY AND SCOPE OF STUDY VISITS

What is the proposed frequency and scope of study visits and, if applicable, the duration of post-trial follow-up? Give a schematic diagram (flow chart) of design, procedures and stages.

2. THE MEDICAL PROBLEM

Which medical problem is to be addressed? What is the novel aspect of the proposed trial? Which principal research questions are to be addressed? Bring them into order indicating major and minor motivations/starting hypotheses of the investigation planned.

2.1 EVIDENCE

Set your trial into perspective. Which trials have been conducted either by you or by others? What is the relevance of their results? Give references to any relevant systematic review(s)³

³ For definition of a systematic review, see Oxman, AD (1994). Checklists for review articles, BMJ; 309; 648-51.

and/or (own) pilot studies, feasibility studies, relevant previous/ongoing trials, case reports/series. If you believe that no relevant previous trials have been done, give details of your search strategy for existing information. This should both detail the background of the starting hypotheses and the feasibility of the trial.

2.2 THE NEED FOR A TRIAL

What impact will the results have on clinical practice or understanding of the proposed intervention or underlying disease? Why is a trial needed now? How will a) the individual patient and b) society/science benefit from the trial?

2.3 STRATEGIES FOR THE DISSEMINATION OF RESULTS

What will be your strategies for the dissemination of results? Indicate how the expected results of the trial will be used; discuss dissemination of results, especially beyond regular journal publication, describe intended measures, detail potential economic impact.

3. JUSTIFICATION OF DESIGN ASPECTS

3.1 CONTROL(S)/COMPARATOR(S)

Justify the choice of control(s)/comparison(s): Is placebo acceptable? Which trials establish efficacy and safety of the chosen control regimen?

3.2 INCLUSION/EXCLUSION CRITERIA

Justify the population to be studied, include reflections on generalizability and representativeness.

3.3 OUTCOME MEASURES

Justify the endpoints chosen: Are there other trials that have utilized this endpoint. Are there any guidelines proposing this endpoint/these endpoints? Discuss the clinical relevance of the outcome measures for the target population. Have the measures been validated? Justify appropriateness and limitations of composite endpoints, if applicable.

Determination of primary and secondary measures

How will primary and secondary endpoints be derived from actual measurements, e.g. how is the figure used in the statistical test calculated from the variables initially measured in the subjects?

3.4 METHODS AGAINST BIAS

Is randomisation feasible? Which prognostic factors need to be regarded in the randomisation scheme and the analysis? What are the proposed practical arrangements for allocating participants to trial groups?

Is blinding possible? If blinding is not possible please explain why and give details of alternative methods to avoid biased assessment of results (e.g. blinded assessment of outcome).

3.5 PROPOSED SAMPLE SIZE / POWER CALCULATIONS

What is the proposed sample size and what is the justification for the assumptions underlying the power calculations? Include a comprehensible, checkable description of the power calculations and sample sizes detailing the outcome measures on which these have been based for both control and experimental groups; give event rates, means and medians, etc., as appropriate. Justify the size of difference that the trial is powered to detect, or in case of a non-inferiority or equivalence study, the size of difference that the trial is powered to exclude. It is important that the sample size calculations take into account anticipated rates of non-compliance and losses to follow up.

Compliance / Rate of loss to follow up

Provide details for assumptions on compliance issues. On what evidence are the compliance figures based?

What is the assumed rate of loss to follow up? On what evidence is the loss to follow up rate based? How will losses to follow up or non-compliance be handled in the statistical analysis?

3.6 FEASIBILITY OF RECRUITMENT

What is the evidence that the intended recruitment rate is achievable (e.g. pilot study)?

a) Pilot study

Has any pilot study been carried out using this design?

b) Achievability of recruitment rate

What is the evidence that the intended recruitment rate is achievable? Demonstrate conclusively the potential for recruiting the required number of suitable subjects (the best piece of evidence being pilot studies and preceding studies in a similar population/same institutions). How did you assess that you can recruit the necessary number of patients in each participating centre? Show justification of numbers of eligible patients per trial site in a table. The recruitment plan should show the projected recruitment including the criteria for the selection of trial sites.

International collaborations

If the proposed trial includes non-German centres or collaboration with organisations in other countries please give full details of funding arrangements agreed or under consideration in the trial protocol. Please detail the power of the German component of the trial, as well on its own as part of the international study.

4. STATISTICAL ANALYSES

What is the proposed strategy of statistical analysis? What is the strategy for analysing the primary outcome? If interim analyses are planned, please specify. Are there any subgroup analyses?

5. ETHICAL CONSIDERATIONS

Give a description of ethical considerations relating to the trial (assessment of risks and benefits, care and protection for research participants, protection of research participants' confidentiality, informed consent process).

6. TRIAL MANAGEMENT

6.1 MAJOR PARTICIPANTS *(please indicate roles of major participants)*

#	Name	Affiliation	Responsibility / Role	Signature
			Principal/Coordinating Investigator	
			...	
			

Please indicate trial expertise of all above-mentioned participants by citing relevant publications and/or specifying major role in ongoing trials (to be identified; max. 5 publications of the last 5 years). Ensure that the team of investigators has the necessary range of disciplines and expertise to carry out the trial.

Professional backgrounds/expertise should be detailed in an appendix to the trial protocol (refer to the respective chapter in the trial protocol).

Who is responsible for statistics? Professional background/expertise⁴ should be given. Though not mandatory, certification is highly desirable.

⁴ e.g. GMDS certificate, <http://www.gmds.de/texte/zertifikate-weiteres.html>; see also: ICH guidance E9 "Statistical Principles of Clinical Trials"

#	Name	Affiliation	Responsibility/Role	Signature
			Trial Statistician/ Responsible for Statistics	

6.2 TRIAL-SUPPORTING FACILITIES

Which trial-specific facilities and other resources are available for conducting the trial?

6.3 QUALITY ASSURANCE/MONITORING

What are the proposed measures for quality assurance? Describe and justify the monitoring strategy (percentage of source data verification, number of items to be monitored, number of monitor visits per trial site).

6.4 SAFETY

Please comment on the planned supervision of the trial (DMSC); give name and affiliation of independent DMSC members.

Arrangements for the management of the trials will vary according to the nature of the trial proposed. However, all should include an element of expert advice and monitoring, that is entirely independent of the principal/coordinating investigator and the medical institution involved. This will normally take the form of a scientific advisory board/trial steering committee (TSC) and/or an independent data monitoring and safety committee (DMSC).

It is recognised that these arrangements may not always be appropriate and the committees needed may vary according to the nature of the trial. Thus, the arrangements for supervision should be detailed and justified. The role of these committees can comprise to monitor and supervise the progress of the trial (including the safety data and the critical efficacy endpoints at intervals), to review relevant information from other sources, to ensure adherence to protocol, to consider interim analyses, to advise whether to continue, modify, or stop a trial, and provide the funding organisations with information and advice.

*Applicants should submit their proposed arrangements for overseeing of the trial and a suggested **membership and affiliations** for the committee(s) (name, title, address and telephone number should be given in the trial protocol). A minimum of 3 members should be named.*

7. REFERENCES

8. TRIAL TIMELINE FLOW/MILESTONES

As funding by BMBF will critically depend on the trial progression according to milestones, please provide a proposal of milestones reflecting planning, recruitment status and data clearing/analysis progress. Include a diagram showing trial stages and milestones.

9. FINANCIAL DETAILS OF THE STUDY

9.1 FINANCIAL SUMMARY

Indicate total duration of the trial, the period of time for which funding is requested, and when funding should begin.

The overall expenditure should be summarized in the table below. Please, provide both man months and € for employment costs and state the requested funds separately for each year of the trial. Funds can only be granted for research activities. Do not include patient care costs.

	Organizational Segment	Institution/ Participant/ Trial Site	No of items/ Kind of equipment/ Explanation	Qualification of staff	TVöD/ BAT	Total months	Total years	Total (€)	y1 (m/€)	y2 (m/€)	y3 (m/€)	y... (m/€)
1	Clinical project management											
2	Project management											
3	Data Management											
4	Biometry											
5	Monitoring		number of visits per site number of days per visit monitoring costs per day total no of visits @ x € each									
6	Trial committees	no of DMSC members	no of meetings @ x €/ p									
7	Meetings/ Travel	no of attendees	no of meetings @ x €/ p									
8	Case payment		examinations per subject/patient hours of staff per subject/patient €/ patient x no of patients									
9	Reference centers		no of samples @ x €									
10	Materials		consumables trial manuals, files, forms									
11	Trial drug		€/ patient									
12	Insurance		€/ patient									
13	Fees											
14	Equipment											
15	Other											
	TOTAL							€	€	€	€	€

m = staff indicated in months; € = other expenditures indicated in Euro; ./p = per person

9.2 EQUIPMENT

Please list larger instruments available to you for the trial. In case you apply for instruments which are available where you work, but which are not at the project's disposal, please give detailed information.

Scientific instrumentation

Scientific instrumentation may require installation and running costs, such as refurbishments in the building, additional laboratory expenses, working materials, maintenance costs and operating staff. These expenses cannot be covered by BMBF funding. Applicants must ensure that such costs are provided by their institution before sending in their project.

Application of instrumentation

Please list all requested instrumentation with price information.

9.3 CO-FINANCING BY INDUSTRY AND/OR OTHER THIRD PARTIES

Co-financing by industry or other third parties is possible if

- the independence of investigators is ensured and
- terms and conditions of the financial commitment are disclosed.

If co-financing is intended the application should briefly describe the type and volume of the intended co-financing, indicating the respective company or other third party.

Details are to be specified in the trial protocol:

- Describe the type and volume of support (including any services or consumables provided free of charge, e.g. drugs for the trial).
- Indicate the amount of support to be provided and assure in writing that the third party will render these services, stating their terms and conditions, if any.
- Assure that the coordinating investigator is independent, in particular with regard to the analysis of the trial and the publication of its results. A statement giving such assurances will be demanded by the funding organizations after the review process is finished.

Please don't make any agreements before notion of award has been made; please contact the funding organisations first! Appropriate agreements on intellectual property, confidentiality, publication of results, property rights should be concluded between all those playing a leading part in the conduct of the trial.

Agreement with manufacturer on variation of authorisation:

If the trial is aimed at extending the indication of a drug, modifying its mode of administration/preparation or dosage, or target population, the manufacturer of the drug must assure in writing that he will undertake to apply for a variation of the authorisation at the Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices) if the trial result is favourable. A corresponding statement should be joined to the protocol.

Reference is made to the legal provisions relevant to cooperation between industry, medical institutions and their staff.⁵

9.4 OTHER FUNDING

In case you have already submitted the same request for financial support or parts hereof to other institutions, please mention this here. Indicate those third parties which will provide funds, free services or consumables such as trial medication.

If this is not the case please declare:

⁵ Detailed information can be found in particular in the "Gemeinsamer Standpunkt zur strafrechtlichen Bewertung der Zusammenarbeit zwischen Industrie, medizinischen Einrichtungen und deren Mitarbeitern" (Common position concerning the consideration of cooperation between industry, medical institutions and their staff from the aspect of criminal law) published by the Verband forschender Arzneimittelhersteller (Association of Research-Based Pharmaceutical Companies) (<http://www.vfa.de/de/vfa/gemeinsamerstandpunkt.html>)

"A request for funding this project has not been submitted to any other addressee. In case I submit such a request I will inform the Federal Ministry of Education and Research immediately".

10. TRIAL PROTOCOL IN ACCORDANCE WITH ICH GCP

Append the trial protocol in English in accordance with ICH GCP (cf. chapter 6 of ICH GCP, "Clinical Trial Protocol and Protocol Amendment(s)"). The topics laid down there may be adjusted slightly to reflect the needs of non-drug trials.

Should you consider any requirement not applicable, relevant or appropriate, a clear statement justifying the omission of the information specified shall be provided on each occasion.

The final version of the protocol has to be submitted to the funding organization together with the statement by the ethics committee after the review process, but prior to any notion of award.

Note: Any potential conflicts must be disclosed in the trial protocol. The rules set forth in the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" have to be observed by analogy (www.thelancet.com).