DLR Projektträger

Bundesministerium für Bildung und Forschung

Leitfaden für die Erstellung von ausführlichen Projektskizzen für klinische Studien zur „Richtlinie zur Förderung klinischer Studien mit hoher Relevanz für die Patientenversorgung“

Version vom 11.01.2022

Dieser Leitfaden stellt die Anforderungen für die Erstellung von beurteilungsfähigen Projektskizzen dar. Er ergänzt die am 12. Mai 2021 im Bundesanzeiger veröffentlichte o. g. Förderrichtlinie (https://www.gesundheitsforschung-bmbf.de/de/13082.php). Er soll offene Fragen im Vorfeld der Einreichung klären.

Projektskizzen, die den Vorgaben der Förderrichtlinie und des folgenden Leitfadens nicht entsprechen, können ohne weitere Prüfung abgelehnt werden.

Es wird dringend empfohlen, zur Beratung mit dem DLR Projektträger Kontakt aufzunehmen. Ansprechpartnerin ist:

Frau Dr. Eva Müller-Fries
Telefon: 0228-3821 2567; E-Mail: klinische-studien@dlr.de

Die Fördermaßnahme wird in enger Abstimmung mit dem Förderkonzept zu Klinischen Studien der Deutschen Forschungsgemeinschaft (DFG) durchgeführt. **Doppeleinreichungen bei DFG und BMBF sind nicht zulässig und führen zum Ausschluss aus dem Verfahren.**

Entscheidungsverfahren

Modul 1: Projektskizzen für explorative oder konfirmatorische klinische Studien

Für Projektskizzen zu explorativen oder konfirmatorischen klinischen Studien sind jeweils zwei fachliche Begutachtungsschritte vorgesehen. Zunächst sind **Projektskizzen (outline proposals)** einzureichen, die von einem unabhängigen Begutachtungsgremium geprüft werden. In diesem ersten Begutachtungsschritt werden die gesundheitspolitische Bedeutung und der patientenbezogene Nutzen der Studien vorrangig bewertet. Außerdem wird die methodisch-wissenschaftliche Qualität bewertet. Einreichende, deren Skizzen durch dieses Gremium positiv bewertet wurden, werden zur Vorlage von **ausführlichen Projektskizzen (full proposals)** aufgefordert. Diese werden in einem zweiten fachlichen Begutachtungsschritt wiederum durch ein unabhängiges, internationales Begutachtungsgremium bewertet.

Inhaltliche Vorgaben für die Projektskizzen

Gefördert werden können:

Modul 1:

Wissenschaftsinitiierte, multizentrische, prospektive, **randomisierte, kontrollierte klinische Studien** zum Wirksamkeitsnachweis von Therapiekonzepten. Jede Studie muss eine Intervention an Patientinnen und / oder Patienten beinhalten und eine konfirmatorische Zielsetzung aufweisen.

Wissenschaftsinitiierte, explorative klinische Studien mit geringen Patientenzahlen, die der direkten Vorbereitung von multizentrischen klinischen Studien mit hohen Patientenzahlen dienen. Jede Studie muss eine Intervention an Patientinnen und / oder Patienten beinhalten. In der Regel sollten wenigstens zwei Prüfzentren eingebunden sein.

Damit gewährleistet ist, dass die Bedürfnisse der Patientinnen und Patienten angemessen berücksichtigt werden, sind sie oder ihre Vertretungen bei allen Projekten in geeigneter Weise zu beteiligen.

Klinische Studien können für einen Zeitraum von bis zu vier Jahren gefördert werden. In begründeten Fällen, in denen die klinische Studie in vier Jahren nicht beendet werden kann, besteht die Möglichkeit, die Studie über diesen Zeitraum hinaus fortzuführen. **Die hier beantragte Studie ist in einem solchen Fall in der Projektskizze bzw. der ausführlichen Projektskizze immer über die gesamte benötigte Laufzeit darzustellen.**

Formale Vorgaben für die Projektskizzen

Modul 1: Projektskizzen für explorative oder konfirmatorische klinische Studien

a) Einreichen von Projektskizzen (outline proposals)

b) Einreichen von ausführlichen Projektskizzen (full proposals)

Einreichende, deren Skizzen im ersten Begutachtungsschritt positiv bewertet wurden, werden zur Vorlage von ausführlichen Projektskizzen aufgefordert. Im Sinne der Vergleichbarkeit sind dafür die Formatvorgaben des Leitfadens und die darin vorgegebene Gliederung verbindlich einzuhalten (s. Abschnitt „Full Application for the Funding of a Confirmatory Clinical Trial“ bzw. „Full Application for the Funding of an Exploratory Clinical Trial“ und des jeweiligen Abschnitts „Appendix“):

- https://projekttraeger.dlr.de/media/gesundheit/GF/CONFIRMATORY_CLINICAL_TRIAL_FULL_APPLICATION_2021.docx

- https://projekttraeger.dlr.de/media/gesundheit/GF/EXPLORATORY_CLINICAL_TRIAL_FULL_APPLICATION_2021.docx

Die ausführlichen Projektskizzen sind ausschließlich elektronisch als pdf-Dokumente einzureichen unter:

https://ptoutline.eu/app/ks2021

Es sind zwei Dokumente vorzulegen:
(a) die ausführliche Projektskizze als pdf-Datei (max. 10 MB) und
(b) der Anhang als pdf-Datei (max. 30 MB).

Allgemeine Hinweise

Nachfolgende Hinweise sind bei der Planung und Einreichung aller Projektskizzen und ausführlichen Projektskizzen zu beachten.

➢ Wissenschaftliche Standards

Die Antragstellenden sind verpflichtet, nationale und internationale Standards zur Qualitätssicherung der klinischen Forschung einzuhalten. Hierzu sind die nachfolgenden Dokumente in der jeweils geltenden Fassung zu berücksichtigen:

- Deklaration von Helsinki,
- ICH-Leitlinie zur Guten Klinischen Praxis (ICH-GCP),
- EU-Richtlinie 2005/28/EG und EU-Verordnung Nr. 536/2014,
- CONSORT-, STARD-, PRISMA- und GRIPP2-Statements.

Zudem sind für klinische Studien die „Grundsätze und Verantwortlichkeiten bei der Durchführung klinischer Studien“ des BMBF verpflichtend zu beachten:
http://www.dlr.de/pt/Portaldata/45/Resources/Dokumente/GF/Grundsaetze_Verantwortlichkeiten_Klinische_Studien.pdf.

Es wird empfohlen, die Arbeitshilfen der TMF (Technologie- und Methodenplattform für die vernetzte medizinische Forschung e.V.) zu verwenden, z. B. zu Datenschutz oder Patienteneinwilligung.

➢ Registrierung

Modul 1: Klinische Studien

Vom BMBF geförderte klinische Studien müssen vor Einschluss des ersten Patienten bzw. der ersten Patientin in einem WHO-kompatiblen Primär-Register registriert werden (z. B. Deutsches Register Klinischer Studien, DRKS). Der hinterlegte Datensatz ist im Verlauf des Vorhabens kontinuierlich zu aktualisieren.

➢ Zugänglichkeit des Studienprotokolls und der Forschungsergebnisse

Modul 1: Klinische Studien

Um Transparenz über die durchgeführte Forschung zu erreichen, ist bei Förderung das Studienprotokoll inklusive aller Dokumentationsformulare (CRF) vor Rekrutierungsbeginn in einer einschlägigen wissenschaftlichen Fachzeitschrift zu veröffentlichen. Des Weiteren müssen die Ergebnisse der Studie innerhalb von einem Jahr nach Schließen der Datenbank in einem WHO-zertifizierten Primär-Register (z. B. im Deutschen Register Klinischer Studien, DRKS) eingestellt werden. Zusätzlich müssen die Ergebnisse der Studie innerhalb eines weiteren Jahres publiziert werden. Dies beinhaltet mindestens die Publikation der Ergebnisse auf einem wissenschaftlichen Kongress und die Publikation der Ergebnisse (auch negativer Ergebnisse) in einer einschlägigen wissenschaftlichen Fachzeitschrift. Die Veröffentlichung des Studienprotokolls sowie der aus dem Forschungsvorhaben resultierenden Ergebnisse soll in einer wissenschaftlichen Zeitschrift so erfolgen, dass der Öffentlichkeit der unentgeltliche elektronische Zugriff (Open Access) auf den Beitrag möglich ist. Für eine Open Access Veröffentlichung der Vorhabenergebnisse können nur solche Zeitschriften ausgewählt werden, deren Artikel unmittelbar mit Erscheinen über das Internet für Nutzer entgeltfrei zugänglich sind und die im jeweiligen Fach anerkannte, strenge Qualitätssicherungsverfahren anwenden. Publikationsgebühren für Open Access Publikationen sind zuwendungsfähig.

Unter Punkt 8 in den Projektskizzen und Punkt 2.4 ist in den ausführlichen Projektskizzen der klinischen Studien zu beschreiben, wie, in welchem Umfang, in welcher Verarbeitungsstufe und in welchem zeitlichen Rahmen die Forschungsdaten zugänglich gemacht werden, um eine sinnvolle Nachnutzung durch Dritte zu ermöglichen (unter Wahrung der Rechte Dritter insbesondere Datenschutz, Urheberrecht; weitere Informationen unter http://www.dfg.de/download/pdf/foerderung/antragstellung/forschungsdaten/guidelines_research_data.pdf). In den ausführlichen Projektskizzen unter Punkt 2.4 ist zudem eine Erklärung zum Thema „Data sharing“ abzugeben, s. auch https://www.aerzteblatt.de/pdf.asp?id=190312.

- **Aktive Beteiligung von Betroffenen und / oder Nutzern**

Eine aktive Einbindung von betroffenen Patientinnen und Patienten, ihren (pflegenden) Angehörigen sowie weiteren relevanten Personen wie z. B. Nutzern und/oder Erbringern medizinischer Dienstleistungen kann die Relevanz und Qualität von Forschung erhöhen („Zielgruppenbeteiligung“).
Patientinnen und Patienten bringen eine einzigartige Sichtweise auf das Forschungsthema ein. Durch eine aktive Patienteneinbindung bei der Identifizierung und Priorisierung von Forschungsfragen und patienten-relevanten Endpunkten kann die durchgeführte Forschung näher an den tatsächlichen Bedürfnissen der Betroffenen ausgerichtet werden. Hierdurch kann sich die Akzeptanz und Unterstützung erhöhen, die die klinische Forschung von Betroffenen erfährt. Durch die Gestaltung von teilnehmerfreundlichen Forschungsbedingungen und die gemeinschaftliche Entwicklung von laienverständlichen Studiendokumenten kann möglicherweise die Effektivität der Forschung und die Rekrutierung von Studienteilnehmerinnen und Studienteilnehmern unterstützt werden. Auch die Datenanalyse kann von einer Patientenbeteiligung profitieren. Beispielsweise können Fehlinterpretationen möglicherweise vermieden oder weitere relevante Zusammenhänge oder Themen identifiziert werden. Nicht zuletzt kann die Einbindung von Betroffenen bei der Dissemination der Ergebnisse die Kommunikation an relevante Zielgruppen unterstützen und dabei helfen, verständliche und wirkungsvolle Botschaften zu senden.
Je nach Forschungsthema kann es sinnvoll sein, Patientinnen und Patienten (oder ggf. auch weitere Zielgruppen) bereits in der Planungs- bzw. Konzeptionsphase klinischer Forschungsprojekte zu beteiligen, beispielsweise indem die Perspektive von Betroffenen in die Identifizierung prioritärer Forschungsfragen, der Auswahl der Interventionen und primären Endpunkte sowie die Entwicklung des späteren Forschungsdesigns einfließt.
Die folgenden, zum Teil internationalen Handreichungen, Leitfäden und Standards für Zielgruppebeteiligung können wertvolle Hinweise liefern, wie die aktive Beteiligung von Patinnen und Patienten gestaltet werden kann (nicht abschließende Auswahl):

Jilani, H.; Rathjen, K.I.; Schilling, I.; Herbon, C.; Scharpenberg, M.; Brannath, W.; Gerhardus, A., 2020: Handreichung zur Patient*innenbeteiligung an klinischer Forschung, Version 1.0, Universität Bremen. Verfügbar unter: http://dx.doi.org/10.26092/elib/229
INVOLVE, Briefing notes for researchers: https://www.nihr.ac.uk/documents/briefing-notes-for-researchers-public-involvement-in-nhs-health-and-social-care-research/27371#Disseminating_research
Stellungnahme der Deutschen Vereinigung für Rehabilitation: “Partizipation an der Forschung” – eine Matrix zur Orientierung; Verfügbar unter: http://dgrw-online.de/wordpress/wp-content/uploads/matrix_ef_1.pdf
A Researcher’s Guide to Patient and Public Involvement https://oxfordbrc.nihr.ac.uk/wp-content/uploads/2017/03/A-Researchers-Guide-to-PPI.pdf
A central resource for Involvement in Health and Social Care. PPI Training. Verfügbar unter: http://engage.hscni.net/ppi-training/training-for-service-users-and-carers/.
Patient-Centered Outcomes Research Institute (PCORI) Engagement Resources: Verfügbar unter: https://www.pcori.org/engagement/engagement-resources#content-4029
PATIENT INVOLVEMENT IN CLINICAL RESEARCH - A guide for Patient Organisations and Patient Representatives. Verfügbar unter: https://www.geneticalliance.org.uk/media/1602/patientspartnerforpatientorgs.pdf
Cochrane Consumer Network: https://consumers.cochrane.org/news/international_network

Mustervorlagen & Erläuterungen

Nachfolgend finden sich Mustervorlagen und Erläuterungen zu den ausführlichen Projektskizzen zu konfirmatorischen bzw. explorativen klinischen Studien:

Mustervorlage & Erläuterungen für ausführliche Projektskizzen für konfirmatorische klinische Studien
Mustervorlage & Erläuterungen für ausführliche Projektskizzen für explorative klinische Studien

Mustervorlage & Erläuterungen für ausführliche Projektskizzen für konfirmatorische klinische Studien

Full Application for the Funding of a Confirmatory Clinical Trial

Note that there are major differences as compared to the previous calls for clinical trials!

To ensure comparability of all submitted full applications please prepare your application in English **not exceeding 17 pages for the headings 1. to 8.** (DIN A4, at least 10 point Arial and 9 point Arial for the synopsis and references, margins of at least 2 cm and single-spaced lines). Structure your application using the headings listed below. Make an entry under each heading.

Please use abbreviations only moderately and do only use common abbreviations. A list of abbreviations (max. ½ page) may be included in the appendix. **Nevertheless, all abbreviations must be introduced at first use.**

Scanned signatures of principal / coordinating investigator and trial statistician are mandatory in section 9. "LIST OF PARTICIPANTS INVOLVED IN THE TRIAL".

1. STUDY SYNOPSIS

APPLICANT/COORDINATING INVESTIGATOR	In case of multiple applicants, the principal investigator / coordinating investigator[1] of the trial who will assume responsibility for conducting the clinical trial, should be listed <u>first</u>. • First name, last name, academic title • Institution and department (complete name) • Postal address • Telephone • E-mail address
TITLE OF STUDY	*Descriptive title identifying the study design, population, and interventions In case of funding this title shall be quoted in the annual reports of the BMBF. Acronym is optional.*
CONDITION	*The medical condition being studied (e.g. asthma, myocardial infarction, depression)*
OBJECTIVE(S)	*Which principal research questions are to be addressed? Specify clearly the primary hypotheses of the trial that determine sample size calculation.*
KEY INCLUSION AND EXCLUSION CRITERIA	<u>Key inclusion criteria:</u> <u>Key exclusion criteria:</u>
INTERVENTION(S)	*Brief description of the experimental and the control treatments or interventions as well as dose and mode of application.* <u>Experimental intervention:</u> <u>Control intervention:</u>

[1] *Zur Definition des "Investigator" siehe "Guideline for Good Clinical Practice" der International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH E6(R2)). 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 multicentre trial." Diese Definition sollte auch für nicht-pharmakologische Studien verwendet werden.*

	Duration of intervention per patient: Follow-up per patient: Experimental and / or control off label or on label in Germany: *if applicable*
OUTCOME(S)	Primary efficacy endpoint: Key secondary endpoint(s): Assessment of safety:
STUDY TYPE	*e.g. randomized, type of masking (single, double, observer blind), type of controls (active / placebo), parallel group / cross-over*
STATISTICAL ANALYSIS	Efficacy: Description of the primary efficacy analysis and population: Safety: Secondary endpoints:
SAMPLE SIZE	To be assessed for eligibility (n = …) To be allocated to trial (n = …) To be analysed (n = …)
TRIAL DURATION	Time for preparation of the trial (months): Recruitment period (months): First patient in to last patient out (months): Time for data clearance and analysis (months): Duration of the entire trial (months):
PARTICIPATING CENTERS	To be involved (n): How many centres will be involved? Signed agreement to participate (n)*: How many centres have signed an agreement to participate? Full list under 9.*
PREVIOUS BMBF PROJECT NUMBER	*If applicable, the BMBF code number of the latest application or of any previous application(s) for project-funding by the BMBF (not other funders) concerning this trial.*

1.1 RESPONSE TO REVIEWERS' COMMENTS

Please summarize in English the assessment of your outline application with all recommendations given. Please respond with a short point-by-point reply separately to each recommendation (2 pages max.). Where necessary, refer to changes made in this full application.

1.2 SUMMARY

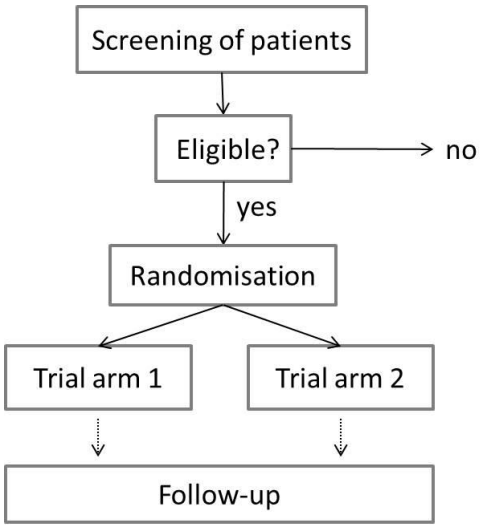
Give a summary of the main aspects of the project; it should not exceed 15 lines (max. 1600 characters incl. blanks). The project summary serves one main goal: It will inform the multidisciplinary committees which make the final decision on your grant, of the principal aspects e.g. goals, design, subjects, expected outcome of your project.

1.3 LAY SUMMARY

Please provide a brief summary (max ½ page) of the envisaged study including the relevance for patients, their families and carers. Summarize the objectives, design, expected outcomes and potential of the findings to translate beyond the research setting. Please note: the lay summary needs to be written as a plain English summary, such that it is clear, easy to understand, and is easily accessible to a broad lay audience. Avoid the use of highly technical terms. This summary will be used for lay persons involved in the review of these proposals. It may be used later on when providing information to the public concerning the variety of research funded within this call.

1.4 INTERVENTION SCHEME / TRIAL FLOW

Describe the intervention scheme in depth and give a schematic diagram (flow chart) of design, procedures and stages. Recommendations for a complete description you may find in the TIDieR checklist and guide. An example of such a diagram is given below:



1.4 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? Please also give a table with time-points of visits and procedures per time-point. Specify items to be recorded on CRF per procedure.

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. This section should detail the background of the starting hypotheses of the trial. Also give evidence why a confirmatory trial is justifiable at this stage.

A description of how you searched for the evidence (databases, search terms, limits) is mandatory: Please indicate the electronic databases searched. MEDLINE, Cochrane Central, the Cochrane library, clinicaltrials.gov, Deutsches Register Klinischer Studien (DRKS) and International Clinical Trials Search Portal (ICTRP) are recommended as a minimum, but other databases may be relevant in special occasions. Include search terms, limits, date of search and time period covered. Provide a narrative summary: 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)[2] and / or pilot studies, feasibility studies, relevant previous / ongoing trials, case reports / series. State what your study adds to the existing body of evidence. Also explain why a confirmatory trial is justified in this case.

A full electronic search strategy for one database, including any limits used, has to be presented in section 12 (max. one page). Guidance concerning search techniques can be found here: https://www.cochrane.de/de/literaturrecherche.
Please note that insufficient clinical evidence precludes funding.[3]

[2] Eine Definition für einen systematischen Review finden Sie unter Cook DJ, Mulrow CD, Haynes RB. Systematic Reviews: Synthesis of Best Evidence for Clinical Decisions. Ann Intern Med 1997; 126 (5): 376-380
[3] vgl. hierzu Clark S and Horton R (2010). Putting research into context – revisited; The Lancet; 376(9734); 10-11

2.2 THE NEED FOR A TRIAL

How significant is the trial in terms of its potential impact of relieving the burden of disease and / or improving human health? What impact will the results have on clinical practice? How will the individual patient benefit from the trial?

2.3 PATIENT AND STAKEHOLDER INVOLVEMENT

Please describe how patient and other relevant stakeholders (e.g. (nursing) relatives, and other relevant groups such as users and / or providers of medical services) will be involved in the planning, conduct and exploitation of results of the trial[4,5]. Please note: Patient involvement is mandatory wherever feasible.

Who?: Which patients, patient representative(s), patients' self-help group(s), patient advocacy group(s) or other relevant stakeholders was / were involved in the planning of the trial? Who is planned to be involved during the conduct of the ongoing trial? Who is planned to be engaged in dissemination of the results?

How? How have patient representative(s), patients' self-help group(s), patient advocacy group(s) or other relevant stakeholders been involved in the planning of the trial? How were the patients' needs, goals, concerns and preferences considered? How will patient representative(s), patients' self-help group(s) or patient advocacy groups be engaged during the conduct of the trial and dissemination of results?

When? When were / are patients, patient representative(s), patients' self-help group(s), patient advocacy group(s) or other relevant stakeholders involved in e. g. developing the main question, developing the trial design, defining endpoints, accompanying the ongoing trial, communicating trial results? Is engagement at specific time points or continuous engagement (including feedback loops) planned?

Patient involvement can be implemented in different stages of the trial and to a different extent. Please justify why your concept is adequate for the planned trial.

2.4 STRATEGIES FOR DATA STORAGE, HANDLING AND THE DISSEMINATION OF RESULTS

Describe how data will be collected / generated and how consistency and quality of data will be controlled and documented. Describe how data will be stored, backed up, managed and curated in the short to medium term. Specify any community agreed or other formal data standard used. Which metadata is produced about the data generated from the research to enable research data to be used by others outside of your own team (taking into account privacy rules and proprietary data), e.g. documentation of methods used to generate the data, analytical and procedural information, provenance of data and their coding, detailed descriptions for variables, records etc.? Provide plans and place for long-term storage and preservation for the research data. Please use existing standards and data repositories where appropriate. See also: http://www.dfg.de/download/pdf/foerderung/antragstellung/forschungsdaten/guidelines_research_data.pdf.

Please provide a data sharing statement, which includes answers to the following questions: Will individual de-identified participant data (including data dictionaries) be shared at all? What data in particular will be shared? Will additional, related documents be available (e.g., study protocol, statistical analysis plan, etc.)? When will the data become available and for how long? By what access criteria will the data be shared (including with whom, for what types of analyses, and by what mechanism)? Further information on the data sharing statement can be found under https://www.nejm.org/doi/full/10.1056/NEJMe1705439.

---

[4] *s. auch eine Einführung von INVOLVE zugehörig zum Britischen National Institute for Health Research, NHS „Briefing note for Researchers": https://www.nihr.ac.uk/documents/briefing-notes-for-researchers-public-involvement-in-nhs-health-and-social-care-research/27371*

[5] *Consider GRIPP2 reporting checklists: tools to improve reporting of patient and public involvement in research" for reporting of patient and public involvement. https://www.equator-network.org/reporting-guidelines/gripp2-reporting-checklists-tools-to-improve-reporting-of-patient-and-public-involvement-in-research/*

Discuss the dissemination of results of the trial, especially beyond regular journal publication.

3. JUSTIFICATION OF DESIGN ASPECTS

Please provide justifications on different design aspects. It is not sufficient to list respective parameters only.

3.1 INCLUSION / EXCLUSION CRITERIA

Justify the population to be studied, include reflections on generalisability and representativeness, specifically with regard to gender and age.

3.2 CONTROL(S) / COMPARATOR(S)

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

3.3 DOSE, MODE AND SCHEME OF INTERVENTION

Justify the dose, the mode and the scheme of the intervention. How does the intervention compare to other interventions for the same condition? For pharmacological studies: Will the trial drugs be readily available for the trial? How will the mode of intervention (e.g. drug or medicinal product) and controls be provided for this study?

3.4 ADDITIONAL TREATMENTS

Please describe the medication(s) / treatment(s) permitted (including rescue medication) and not permitted before and / or during the trial, if applicable.

3.5 OUTCOME MEASURES

Justify the endpoints chosen: Are there other trials that have utilized this endpoint? Are there any guidelines proposing this endpoint / these endpoints? Patient-relevant endpoints have to be prioritized, if possible. Discuss the clinical relevance and as well the relevance for the patient of the outcome measures for the target population or the patient. 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?

3.6 METHODS AGAINST BIAS

Justify the randomisation scheme. 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? Will trial site effects be considered in randomisation? Please justify if randomisation is not feasible.

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).

3.7 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, the software used for sample size calculation 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. Give evidence / references for the estimated effect size. Sample size calculations need to 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?

3.8 FEASIBILITY OF RECRUITMENT

What is the evidence that the intended recruitment rate is achievable?

a) Pilot study
Has any pilot study been carried out using this design?

b) Achievability of recruitment rate
Demonstrate conclusively the potential for recruiting the required number of suitable subjects (the best piece of evidence being pilot studies and preceding trials in a similar population / same institutions). Comment on the prevalence of the disease, the access to patients and their willingness to be randomized in a trial. 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.

Note that - in case of funding - pre-study-visits will be mandatory to confirm the estimated recruitment numbers.

International collaborations
If the proposed trial includes foreign centres or collaboration with organisations in other countries please give full details of funding arrangements agreed or under consideration.

3.9 STOPPING RULES

Please specify the “stopping rules” or “discontinuation criteria”

a) for the individual patient,

b) for participating centers, which fail to include the estimated number of patients and

c) for the whole trial.

4. STATISTICAL ANALYSES

What is the proposed strategy of statistical analysis? If multiple hypotheses are foreseen for confirmatory testing what is the procedure to ensure Type I error control and what will be the primary data analysis set (e.g. ITT-population in case of superiority RCT). What is the strategy for analysing the primary outcome? If applicable, how will multiple primary endpoints be analysed statistically? If interim analyses are planned, please specify. Are there any subgroup analyses? How will missing data and subjects withdrawn from the trial be handled statistically?

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. QUALITY ASSURANCE, SAFETY AND MANAGEMENT STRUCTURE

6.1 QUALITY ASSURANCE / MONITORING

What are the proposed measures for quality assurance? Which institution will perform the monitoring? Which SOPs will be utilized? Describe and justify the monitoring strategy (percentage of source data verification, number of monitor visits per trial site).

Please note: The funding agency (DLR-PT) will insist on the conduct of pre-trial visits. Those visits must be carried out before the trial begins in each recruiting centre by independent bodies, if

feasible also accompanied by the PI or a member of the steering committee. Visiting an excess number of sites to allow selection of the most suitable sites is possible. Please make sure to include these as a milestone into the time plan and into the budget. The report of the results and the consequences drawn from these visits by the steering committee or the PI must be documented and can be requested by the funding agency. Note that delays in patient recruitment may lead to discontinuation of funding, especially if reports from pre-study visits and monitoring visits addressing possible shortcomings were not adequately dealt with in time. If conducting the pre-study visits is not possible or feasible, this has to be well justified in the proposal.

6.2 SAFETY / PHARMACOVIGILANCE

Describe and justify briefly the proposed strategy for the assessment of patients' safety in the trial (Monitoring of adverse events, documentation, reporting procedures, etc).

6.3 MANAGEMENT STRUCTURE AND PROCEDURES

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

It is recognised that these arrangements may not always be appropriate and the committees needed may vary according to the nature of the study. 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 agency with information and advice.

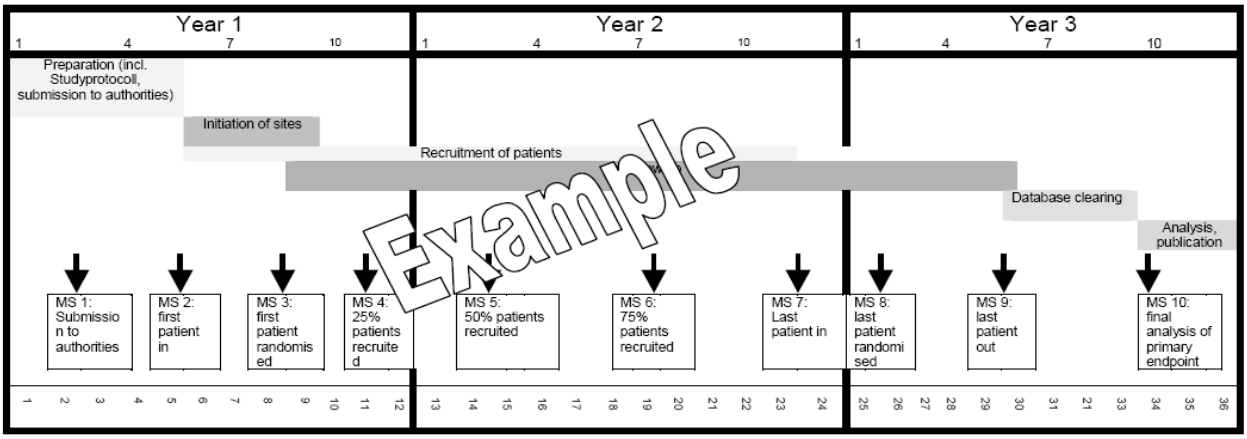
Applicants should submit their proposed arrangements for overseeing of the trial and a suggested **membership** for the committee(s). A minimum of 3 members should be listed under point 9.

7. REFERENCES

For your references please use the Vancouver style (the full title of the publication must be displayed; please find further information here: International Committee of Medical Journal Editors. Uniform Requirements for Manuscripts submitted to Biomedical Journals. NEJM 1997;336:309-15).

8. TRIAL TIMELINE FLOW

As funding by BMBF will critically depend on the study progression according to milestones, please provide a diagram reflecting preparation, pre-study-visits and initiation of centres, recruitment, follow-up and data cleaning / analysis. An example of such a diagram is given below.



9. LIST OF PARTICIPANTS INVOLVED IN THE TRIAL

Trial Sponsor				
Trial Management				
#	Name	Affiliation	Responsibility/Role	Signature
Trial statistician				
#	Name	Affiliation		Signature
Trial Supporting facilities *(reference laboratories, pharmacies etc.)*				
#	Name	Affiliation	Responsibility/Role	

Recruiting centres *(please provide signatures on declaration of commitment)*							
#	Name	Affiliation *(only institution and city, no complete address)*	No. of patients with condition relevant to the trial seen in the last 12 months	No. of these patients fulfilling the inclusion criteria	No. of these patients which would approx. agree to participate in the trial per year	Expected no. of patients recruited for the complete trial	Source of these figures
Total sum of recruited patients					Σ =		

Data Safety and Monitoring Board (DSMB)		
#	Name	Affiliation *(only institution and city, no complete address)*

Other participating groups / bodies *(e.g. steering committee in international trials)*			
#	Name	Affiliation	Responsibility/Role

Include a tabular scientific CV (**two pages**) for the principal/ coordinating investigator. Include also tabular scientific CVs (**one page**) for academic staff members playing a leading role (i.e. co-applicants, members of trial management, trial statistician; not all collaborating partners at all trial centres) under 11 (not separately in the appendix).

Recruiting centres must detail their commitment on a separate sheet (cf. appendix) as provided by the funding agency.
A final version of the trial protocol has to be submitted to the funding agency together with the statement by the ethics committee after the review process. While funding for a preparatory phase might be provided upon the general funding decision, funding of the actual trial can only be provided if all necessary formal and legal requirements are met.

Note: Any potential conflicts of interest must be disclosed in the appendix. The rules set forth in the "Guidelines for avoiding conflicts of interest" by the German Research Foundation (http://www.dfg.de/formulare/10_201/). These guidelines must also be considered when selecting members for the Data Safety and Monitoring Board.

10. FINANCIAL DETAILS OF THE TRIAL

Funds can only be granted for research activities. Do not include patient care costs. The table submitted should detail resources requested clearly yet briefly.

The funds applied for should correspond to defined tasks and each task should be attributed to its respective resources. Please use the tables below.
Also list tasks for which you do not request funding. In these cases, indicate the third parties which provide financial support, free services or consumables e.g. trial-related drugs and indicate their name(s) under separate headings (see also chapter 10.4).

10.1 COMMERCIAL INTEREST

Please justify, why this trial should be funded by a public funding agency and describe any potential commercial interest of a company in the results of the trial or explain why no such interest exists. Note that direct substantial commercial interest of a single company in the results of the trial precludes funding.

10.2 FINANCIAL PLAN

Indicate total duration of the trial, the period of time for which funding is requested and when funding should begin. Funding will be granted for up to 4 years; in the case of longer trials, funding will be continued after a positive interim evaluation.
The overall expenditure should be summarized in the table below (approximately 2 pages). Indicate amounts in € in the column "Total (€)". If duration of the total trial is longer than 4 years, indicate funds requested for years 1-4 and (if applicable) for years 5-end. Please provide man months for staff and € for all other expenditures needed in each funding period.

Please briefly justify the requested resources regarding each single task / item.

Trial stages and tasks associated with each task / item should be listed in the second column of the financial plan. You may list the individual tasks separately for each participating trial site or institute, if adequate. In the third column, please explain and justify the funds necessary for carrying out the individual tasks. Explanations given should be concise and clear to make the table easier to read. Where necessary, itemise more detailed justifications below the table, referring to the number of the individual task.

State the financial resources required of the trial in the other columns. For each individual task, indicate the man months required, using one line for each level of salary; list necessary consumables ("Sachmittel") in a separate column.

In cases where subcontracts are foreseen, applicants should assess on a case-by-case basis whether value added tax must be considered and include this in their calculations. **Adding value added tax after the evaluation of the proposal will not be possible anymore. Thus, carefully plan subcontracts and requested funds for those now.**

Costs for tasks directly associated with the individual subject must be **detailed and justified** and pooled into a fixed rate per case, as far as reasonably possible. The individual tasks including these case payments should be highlighted (e.g. by shading the relevant lines in the table).

Payment of the fixed rate per case to the participating trial centres by the principal investigator/applicant should be made in instalments. **Important: please consider that case payments may also be subject to value added tax**.

	Organizational segment / activity / task	Explanation / Comments / Items	Total				Year 1-4 (man months and €)[6]	Year 5-x (man months and €) [19]
			Staff			Consumables (€)		
			TV-L TV-Ä	Months [7]	€			
1	**Clinical Project Management**							
2	**Project Management**							
3	**Patient Involvement**	e.g. Workshops, Focus Groups, Questionnaires						
4	**Data Management**							
5	**Biometry**							
6	**Quality Assurance/ Monitoring**	number of visits per site (incl. pre-study, initiation, interim and close-out visits) mean number of days per visit (incl. preparation/ postprocessing) mean travel time per visit monitoring costs per day total no of days @ x € each						
7	**Safety / Pharmaco-vigilance**							
8	**Trial Committees**	no. of meetings @ x € / p						
9	**Meetings / Travel**	no. of meetings @ x € / p travel costs monitoring						
10	**Case Payment**	Assays / examinations per patient hours of staff per patient € / patient x no of patients						
11	**Reference Centers**	no. of samples@ x €						
12	**Materials**	Consumables, trial manuals, files, forms						
13	**Trial Drug**	€ / patient						

Only fill in these two columns if the trial duration exceeds 4 years

[6] *Only fill in these two columns if the trial duration exceeds 4 years.*
[7] *Please indicate full-time equivalents*

14	**Insurance**	€ / patient						
15	**Fees**							
16	**Equipment**	> 410 €						
17	**Publications**	Please note that only resources for open access publications will be granted						
18	**Other**							

TOTAL resources requested for the whole trial (year 1-x) € [8]	**Requested resources for years 1-4**	**Requested resources for years 5-x**
€	€	€

[8] *Indicate the requested funding without overhead ("Projektpauschale").*

10.3 EQUIPMENT

Please list all requested research equipment. Explain why the equipment is essential to the project. Note that equipment commonly in use at the research institution (Grundausstattung) cannot be granted.

10.4 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.

- 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 BMBF after the review process is finished.

Please don't make any agreements before notion of award has been made; please contact the project management agency (DLR-PT) 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.

10.5 OTHER FUNDING

In case you have already submitted the same request for financial support or parts hereof to other institutions or the BMBF, 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:
"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".

11. CVs OF MAJOR PARTICIPANTS

11.1 PRINCIPAL / COORDINATING INVESTIGATOR

Include a tabular scientific CV (max. two pages) for the principal / coordinating investigator containing a list of the last five clinical trials by him/her and their reporting status with regard to registration of the trial, publication of the trial protocol and of major results. Explain where trials have remained unreported.

11.2 OTHER MAJOR PARTICIPANTS

Include tabular scientific CVs (one page) for other academic staff members playing a leading role (i.e. co-applicants, members of trial management, trial statistician; not all collaborating partners at all trial centres) including a list of a maximum of 5 publications on clinical trials by him/her that have appeared during the last five years.

12. SEARCH STRATEGY

To substantiate the evidence presented in section 2.1, please present the full search strategy for one electronic database (e.g. MEDLINE, the Cochrane library or clinicaltrials.gov) including any limits used, such that it could be repeated. Indicate filters used. Present the search strategy only, do not provide further explanations. The narrative of the results is to be presented under section 2. Guidance concerning search techniques can be found in the following document: https://www.cochrane.de/de/literaturrecherche.

Example for a full search strategy in MEDLINE (conducted to identify randomized controlled, blinded trials of antipsychotic drugs in treatment resistant patients with schizophrenia):

Search strategy for Medline (30th June 2013)

1 exp Schizophrenia/ (86112)
2 exp Psychotic Disorders/ (38267)
3 schizo$.mp. (127884)
4 or/1-3 (153641)
5 ("treatment resist$" or "therapy resist$" or "drug resist$" or "chemical resist" or "treatment refract$" or "treatment fail$" or nonrespon$ or non-respon$ or "non respon$" or "not respon$" or "no respon$" or "partial respon$" or "partially respon$" or "incomplete respon$" or "incompletely respon$" or unrespon$ or "failed to respond" or "failed to improve" or "failure to respon$" or "failure to improve" or "failed medication$" or refractory or resistant or (inadequate$ adj3 respon$)).mp. (621509)
6 exp Drug Resistance/ (253660)
7 5 or 6 (667475)
8 exp Antipsychotic Agents/ (122182)
9 antipsychoti$.mp. (50055)
10 neurolept$.mp. (20926)
11 benperidol/ or chlorpromazine/ or chlorprothixene/ or clopenthixol/ or Clopenthixol/ or clozapine/ or droperidol/ or flupenthixol/ or fluphenazine/ or fluspirilene/ or haloperidol/ or iloperidone/ or loxapine/ or mesoridazine/ or Methotrimeprazine/ or molindone/ or olanzapine/ or Penfluridol/ or Perazine/ or perphenazine/ or pimozide/ or prochlorperazine/ or promazine/ or promethazine/ or quetiapine/ or Reserpine/ or risperidone/ or sulpiride/ or thioridazine/ or thiothixene/ or trifluoperazine/ or Trifluperidol/ or triflupromazine/ or Veralipide/ or Tiapride Hydrochloride/ (69795)
12 (acetophenazine or amisulpride or aripiprazole or asenapine or benperidol or bromperidol or butaperazine or carpipramine or chlorproethazine or chlorpromazine or chlorprothixene or clocapramine or clopenthixol or clozapine or cyamemazine or dixyrazine or droperidol or fluanisone or flupehenazine or flupenthixol or fluphenazine or fluspirilene or haloperidol or iloperidone or levomepromazine or levosulpiride or loxapine or lurasidone or melperone or mesoridazine or molindone or moperone or mosapramine or olanzapine or oxypertine or paliperidone or penfluridol or perazine or pericyazine or perphenazine or pimozide or pipamperone or pipothiazine or prochlorperazine or promazine or promethazine or prothipendyl or quetiapine or remoxipiride or reserpine or risperidone or sertindole or stelazine or sulpiride or sultopride or thiopropazate or thioproperazine or thioridazine or thiothixene or tiapride or trifluoperazine or trifluperidol or triflupromazine or veralipide or ziprasidone or zotepine or zuclopenthixol).mp. (93792)
13 or/8-12 (149852)
14 4 and 7 and 13 (3026)
15 exp clinical trial/ (785982)
16 exp randomized controlled trials/ (102420)
17 exp cross-over studies/ (35635)
18 randomized controlled trial.pt. (384946)
19 clinical trial.pt. (501097)
20 controlled clinical trial.pt. (89142)
21 (clinic$ adj2 trial).mp. (597724)
22 (random$ adj5 control$ adj5 trial$).mp. (507275)
23 (crossover or cross-over).mp. (66025)
24 ((singl$ or double$ or trebl$ or tripl$) adj (blind$ or mask$)).mp. (179088)
25 randomi$.mp. (582908)
26 (random$ adj5 (assign$ or allocat$ or assort$ or reciev$)).mp. (165555)
27 or/15-26 (1088679)
28 14 and 27 (1048)

APPENDIX

In addition to the declarations of commitment of participating centers, only a list of abbreviations (max. ½ page) and letters of support by patients or patient representatives supporting the requested trial are allowed in the appendix. These letters should best be written in English and should provide a clear and detailed statement on how and by whom the trial will be supported in its planning, conduct and result dissemination. Do not submit any other appendices (e.g. letter of intent / letter of support by other parties).

DECLARATIONS OF COMMITMENT OF PARTICIPATING CENTRES

Please use the template provided to declare the commitment of each participating centre (including the centre of the principal investigator). The template is to be signed personally by the investigator at the respective site (as named in the list of participants involved in the trail; see heading 9. of the full proposal).

Note: Only fully completed forms will be used for the assessment of recruitment feasibility in the review process. Individual estimation of recruitment figures is not regarded as a reliable source. Reported recruitment figures will be checked in case of funding (pre-study visits). In case of inconsistencies between self-assessment and checked numbers, the principal investigator will have to react appropriately and timely.

Note also that delays in patient recruitment may lead to discontinuation of funding, especially if reports from pre-study visits and monitoring visits addressing possible shortcomings were not adequately dealt with in time.

Name of investigator:
Institution:

Information on the clinical trial *(according to the full proposal)*[1]

Trial title:	
Inclusion criteria:	
Exclusion criteria:	
recruitment period (months):	

Strategy for the determination of recruitment figures

How many patients with the condition specified above have you seen in your institution during the last 12 months?	
How many of these patients would fulfil the inclusion criteria of the above mentioned trial?	
How many of these patients would approximately agree to participate in the above named clinical trial per year?	
How many patients will approximately be recruited during the entire trial?	

Which source did you use for the estimation of potential participants in the above named clinical trial?

☐ Individual estimation
☐ Hospital data management system
☐ Patient registry
☐ Others
If others: please specify

Are there any other ongoing clinical trials/ projects competing for the same patients? ☐ yes ☐ no

If yes: How will this affect recruitment for the above-named clinical trial?

Commitment to participate
I hereby agree to participate in the above-named clinical trial and support the trial by recruiting patients.

_____
Date / Signature [2]

Conflicts of Interest
I hereby declare that I have no conflict of private, economical or financial interests[3] with regard to the above mentioned clinical trial and the investigational drugs that will be used. I have no patents, whether planned, pending or issued, broadly relevant to the work.

_____
Date / Signature [2]

---

[1] *Delete italic text at completion of the template.*

[2] *Note: This document is to be signed personally by the investigator at the respective site (as named in the list of participants involved in the trial; see 9. in the full proposal), do not submit facsimiles*

[3] *Any potential conflicts of interest must be disclosed in the appendix. The rules set forth in the "Guidelines for avoiding conflicts of interest" by the German Research Foundation (http://www.dfg.de/formulare/10_201/).*

Mustervorlage & Erläuterungen für ausführliche Projektskizzen für exploratorische klinische Studien

Full Application for the Funding of an Exploratory Clinical Trial

To ensure comparability of all submitted full applications please prepare your application in English **not exceeding 17 pages for the headings 1. to 8.** (DIN A4, at least 10 point Arial and 9 point Arial for the synopsis and references, margins of at least 2 cm and single-spaced lines). Structure your application using the headings listed below. Make an entry under each heading.

Please use abbreviations only moderately and do only use common abbreviations. A list of abbreviations (max. ½ page) may be included in the appendix. **Nevertheless, all abbreviations must be introduced at first use.**

Scanned signatures of principal / coordinating investigator and trial statistician are mandatory in section 9. "LIST OF PARTICIPANTS INVOLVED IN THE TRIAL".

1. STUDY SYNOPSIS

APPLICANT / COORDINATING-INVESTIGATOR	In case of multiple applicants, the principal investigator / coordinating investigator[9] of the trial who will assume responsibility for conducting the clinical trial, should be listed first. • First name, last name, academic title • Institution and department (complete name) • Postal address • Telephone • E-mail address
TITLE OF STUDY	*Descriptive title identifying the study design, population, and interventions. In case of funding this title shall be quoted in the annual reports of the BMBF. Acronym is optional.*
CONDITION	*The medical condition being studied (e.g. asthma, myocardial infarction, depression).*
OBJECTIVE(S)	*Which principal research questions are to be addressed? Specify clearly the primary hypotheses of the trial that determine sample size calculation.*
KEY INCLUSION AND EXCLUSION CRITERIA	Key inclusion criteria: Key exclusion criteria:
INTERVENTION(S)	*Brief description of the experimental and the control treatments or interventions as well as dose and mode of application.* Experimental intervention: Control intervention: Duration of intervention per patient:

[9] *Zur Definition des "Investigator" siehe "Guideline for Good Clinical Practice" der International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH E6(R2)). 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 multicentre trial." Diese Definition sollte auch für nicht-pharmakologische Studien verwendet werden.*

	Follow-up per patient: Experimental and / or control off label or on label in Germany: *if applicable*
OUTCOME(S)	Primary efficacy endpoint: Key secondary endpoint(s): Assessment of safety:
STUDY TYPE	*e.g. randomized, type of masking (single, double, observer blind), type of controls (active / placebo), parallel group / cross-over*
STATISTICAL ANALYSIS	Efficacy: Description of the primary efficacy analysis and population: Safety: Secondary endpoints:
SAMPLE SIZE	To be assessed for eligibility (n = …) To be allocated to trial (n = …) To be analysed (n = …)
TRIAL DURATION	Time for preparation of the trial (months): Recruitment period (months): First patient in to last patient out (months): Time for data clearance and analysis (months): Duration of the entire trial (months):
PARTICIPATING CENTERS	To be involved (n): How many centres will be involved? Please note that at least two centers should be involved. Signed agreement to participate (n)*: How many centres have signed an agreement to participate? Full list under 9.*
PREVIOUS BMBF PROJECT NUMBER	*If* applicable, the BMBF code number of the latest application or of any previous application(s) for project-funding by the BMBF (not other funders) concerning this trial.

1.1 RESPONSE TO REVIEWERS' COMMENTS

Please summarize in English the assessment of your outline application with all recommendations given. Please respond with a short point-by-point reply separately to each recommendation (2 pages max.). Where necessary, refer to changes made in this full application.

1.2 SUMMARY

Give a summary of the main aspects of the project; it should not exceed 15 lines (max. 1600 characters incl. blanks). The project summary serves one main goal: 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.

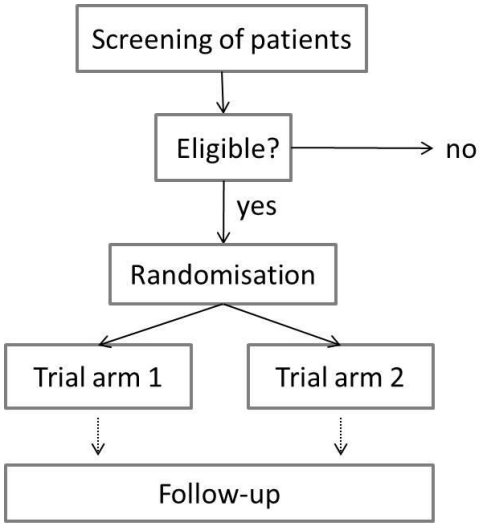
1.3 LAY SUMMARY

Please provide a brief summary (max ½ page) of the envisaged study including the relevance for patients, their families and carers. Summarize the objectives, design, expected outcomes and potential of the findings to translate beyond the research setting. Please note: the lay summary needs to be written as a plain English summary, such that it is clear, easy to understand, and is easily accessible to a broad lay audience. Avoid the use of highly technical terms. This summary will be used **for lay persons involved in the review of these proposals. It may be used later**

on when providing information to the public concerning the variety of research funded within this call.

1.4 INTERVENTION SCHEME / TRIAL FLOW

Describe the intervention scheme in depth and give a schematic diagram (flow chart) of design, procedures and stages. Recommendations for a complete description you may find in the TIDieR checklist and guide. An example of such a diagram is given below:



1.4 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? Please also give a table with time-points of visits and procedures per time-point. Specify items to be recorded on CRF per procedure.

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 and emphasize the link that is missing for the performance of a confirmatory trial.

2.1 EVIDENCE

Set your trial into perspective. This section should detail the background of the starting hypotheses of the trial. How does this trial inform a subsequent confirmatory trial? Describe the exploratory aspects of this trial and how and in which aspects this exploratory trial informs the subsequent confirmatory trial.

A description of how you searched for the evidence (databases, search terms, limits) is mandatory: Please indicate the electronic databases searched. MEDLINE, Cochrane Central, the Cochrane library, clinicaltrials.gov, Deutsches Register Klinischer Studien (DRKS) and International Clinical Trials Search Portal (ICTRP) are recommended as a minimum, but other databases may be relevant in special occasions. Include search terms, limits, date of search and time period covered. Provide a narrative summary: 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)[10] and / or pilot studies, feasibility studies, relevant previous / ongoing trials, case reports / series. State what your study adds to the existing body of evidence.

[10] *Eine Definition für einen systematischen Review finden Sie unter Cook DJ, Mulrow CD, Haynes RB. Systematic Reviews: Synthesis of Best Evidence for Clinical Decisions. Ann Intern Med 1997; 126 (5): 376-380*

A full electronic search strategy for one database, including any limits used, has to be presented in section 12 (max. one page). Guidance concerning search techniques can be found in the following document: https://www.cochrane.de/de/literaturrecherche.
Please note that insufficient clinical evidence precludes funding.[11]

2.2 THE NEED FOR A TRIAL

How significant is the here proposed trial in terms of its potential impact of relieving the burden of disease and / or improving human health? What impact will the results have on clinical practice or understanding of the proposed intervention? How will the individual patient benefit from the trial?

2.3 PATIENT AND STAKEHOLDER INVOLVEMENT

Please describe how patient and other relevant stakeholders (e.g. (nursing) relatives, and other relevant groups such as users and / or providers of medical services) will be involved in the planning, conduct and exploitation of results of the trial[12,13]. Please note: Patient involvement is mandatory wherever feasible.

Who?: Which patients, patient representative(s), patients' self-help group(s), patient advocacy group(s) or other relevant stakeholders was / were involved in the planning of the trial? Who is planned to be involved during the conduct of the ongoing trial? Who is planned to be engaged in dissemination of the results?

How? How have patient representative(s), patients' self-help group(s), patient advocacy group(s) or other relevant stakeholders been involved in the planning of the trial? How were the patients' needs, goals, concerns and preferences considered? How will patient representative(s), patients' self-help group(s) or patient advocacy groups be engaged during the conduct of the trial and dissemination of results?

When? When were / are patients, patient representative(s), patients' self-help group(s), patient advocacy group(s) or other relevant stakeholders involved in e. g. developing the main question, developing the trial design, defining endpoints, accompanying the ongoing trial, communicating trial results? Is engagement at specific time points or continuous engagement (including feedback loops) planned?

Patient involvement can be implemented in different stages of the trial and to a different extent. Please justify why your concept is adequate for the planned trial.

2.4 STRATEGIES FOR DATA STORAGE, HANDLING AND THE DISSEMINATION OF RESULTS

Describe how data will be collected / generated and how consistency and quality of data will be controlled and documented. Describe how data will be stored, backed-up, managed and curated in the short to medium term. Specify any community agreed or other formal data standard used. Which metadata is produced about the data generated from the research to enable research data to be used by others outside of your own team (taking into account privacy rules and proprietary data), e.g. documentation of methods used to generate the data, analytical and procedural information, provenance of data and their coding, detailed descriptions for variables, records etc.? Provide plans and place for long-term storage and preservation for the research data. Please use existing standards and data repositories where appropriate. See also: http://www.dfg.de/download/pdf/foerderung/antragstellung/forschungsdaten/guidelines_research_data.pdf.

Please provide a data sharing statement, which includes answers to the following questions: Will individual deidentified participant data (including data dictionaries) be shared at all? What data in

---

[11] *vgl. hierzu Clark S and Horton R (2010). Putting research into context – revisited; The Lancet; 376(9734); 10-11*

[12] *s. auch eine Einführung von INVOLVE zugehörig zum Britischen National Institute for Health Research, NHS „Briefing note for Researchers": https://www.nihr.ac.uk/documents/briefing-notes-for-researchers-public-involvement-in-nhs-health-and-social-care-research/27371*

[13] *Consider GRIPP2 reporting checklists: tools to improve reporting of patient and public involvement in research" for reporting of patient and public involvement. https://www.equator-network.org/reporting-guidelines/gripp2-reporting-checklists-tools-to-improve-reporting-of-patient-and-public-involvement-in-research/*

particular will be shared? Will additional, related documents be available (e.g., study protocol, statistical analysis plan, etc.)? When will the data become available and for how long? By what access criteria will the data be shared (including with whom, for what types of analyses, and by what mechanism)? Further information on the data sharing statement can be found under https://www.nejm.org/doi/full/10.1056/NEJMe1705439.

Discuss the dissemination of results of the trial, especially beyond regular journal publication. Describe the strategy to engage other trial sites for participation in the following confirmatory trial.

3. JUSTIFICATION OF DESIGN ASPECTS

Please provide justifications on different design aspects and explain how they inform the design of the subsequent confirmatory trial. It is not sufficient to list respective parameters only.

3.1 INCLUSION / EXCLUSION CRITERIA

Justify the population to be studied, include reflections on generalisability and representativeness, specifically with regard to gender and age.

3.2 CONTROL(S) / COMPARATOR(S)

Justify the choice of control(s) / comparison(s): Is placebo acceptable? Is there a gold standard? Which previous (animal) studies establish efficacy and safety of the chosen control regimen?

3.3 DOSE, MODE AND SCHEME OF INTERVENTION

Justify the dose (finding), the mode and the scheme of the intervention. How does the intervention compare to other interventions for the same condition? For pharmacological studies: Will the trial drugs be readily available for the trial? How will the mode of intervention (e.g. drug or medicinal product) and controls be provided for this study?

3.4 ADDITIONAL TREATMENTS

Please describe the medication(s) / treatment(s) permitted (including rescue medication) and not permitted before and / or during the trial, if applicable.

3.5 OUTCOME MEASURES

Justify the endpoints chosen. Have the measures been validated? Are there other trials that have utilized this endpoint? Are there any guidelines proposing this endpoint / these endpoints? What relevance does this endpoint have for the subsequent confirmatory trial? Discuss the clinical relevance and as well the relevance for the patient of the outcome measures for the target population or the patient. Justify appropriateness and limitations of composite / surrogate 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?

3.6 METHODS AGAINST BIAS

Justify the randomisation scheme. 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? Will trial site effects be considered in randomisation? Please justify if randomisation is not feasible.

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).

3.7 PROPOSED SAMPLE SIZE / POWER CALCULATIONS

What is the proposed sample size and what is the justification for the assumptions underlying the power calculations? How do these assumptions relate to the assumed effect size addressed in the subsequent confirmatory trial? 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, the software used for sample size calculation 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. Give evidence / references for the estimated effect size. Sample size calculations need to take into account anticipated rates of non-compliance and losses to follow up.

Please note: various approaches may be eligible to justify sample size calculation. In this exploratory trial, sample size calculation must not necessarily relate to a clinical endpoint, but the impact on the subsequent confirmatory trial should be clarified.

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?

If the proposed sample size is not based on statistical calculation, please justify why another approach has been chosen and why the proposed sample size will be adequate to answer the objective of the trial.

3.8 FEASIBILITY OF RECRUITMENT

What is the evidence that the intended recruitment rate is achievable?

a) Pilot study
Has any pilot study been carried out using this design?

b) Achievability of recruitment rate
Demonstrate conclusively the potential for recruiting the required number of suitable subjects (the best piece of evidence being pilot studies and preceding trials in a similar population / same institutions). Comment on the prevalence of the disease, the access to patients and their willingness to be randomized in a trial. 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.

Note that - in case of funding - pre-study-visits will be mandatory to confirm the estimated recruitment numbers.

International collaborations
If the proposed trial includes foreign centres or collaboration with organisations in other countries please give full details of funding arrangements agreed or under consideration.

3.9 STOPPING RULES

Please specify the “stopping rules” or “discontinuation criteria”

a) for the individual patient,

b) for participating centers, which fail to include the estimated number of patients and

c) for the whole trial.

3.10 CONDITIONS FOR PROCEEDING WITH A SUBSEQUENT CONFIRMATORY TRIAL

The trial has to be directly associated to or preparation of a subsequent confirmatory trial. Describe the exploratory aspects of this trial and how ad in which aspects this exploratory trial informs the subsequent confirmatory trial. How does the exploratory trial match the design of the confirmatory trial and its anticipated clinical impact and relevance for the patients. A defined criterion of success is needed that indicates the success of the exploratory trial and that needs to be fulfilled for transferring the here proposed approach to a confirmatory trial or for dismissing the proposed interventional approach.

4. STATISTICAL ANALYSES

What is the proposed strategy of statistical analysis? What is the strategy for analysing the primary outcome? If applicable, how will multiple primary endpoints be analysed statistically? If interim analyses are planned, please specify. Are there any subgroup analyses? Discuss the robustness of your results e.g. with respect to unavoidable incomplete or missing data.

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. QUALITY ASSURANCE, SAFETY AND MANAGEMENT STRUCTURE

6.1 QUALITY ASSURANCE / MONITORING

What are the proposed measures for quality assurance? Which institution will perform the monitoring? Which SOPs will be utilized? Describe and justify the monitoring strategy (percentage of source data verification, number of monitor visits per trial site).

Please note: The funding agency (DLR-PT) will insist on the conduct of pre-trial visits. Those visits must be carried out before the trial begins in each recruiting centre by independent bodies, if feasible also accompanied by the PI or a member of the steering committee. Visiting an excess number of sites to allow selection of the most suitable sites is possible. Please make sure to include these as a milestone into the time plan and into the budget. The report of the results and the consequences drawn from these visits by the steering committee or the PI must be documented and can be requested by the funding agency. Note that delays in patient recruitment may lead to discontinuation of funding, especially if reports from pre-study visits and monitoring visits addressing possible shortcomings were not adequately dealt with in time. If conducting the pre-study visits is not possible or feasible, this has to be well justified in the proposal.

6.2 SAFETY / PHARMACOVIGILANCE

Describe and justify briefly the proposed strategy for the assessment of patients' safety in the trial (Monitoring of adverse events, documentation, reporting procedures, etc).

6.3 MANAGEMENT STRUCTURE AND PROCEDURES

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

It is recognised that these arrangements may not always be appropriate and the committees needed may vary according to the nature of the study. 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 agency with information and advice.

Applicants should submit their proposed arrangements for overseeing of the trial and a suggested **membership** for the committee(s). A minimum of 3 members should be listed under point 9.

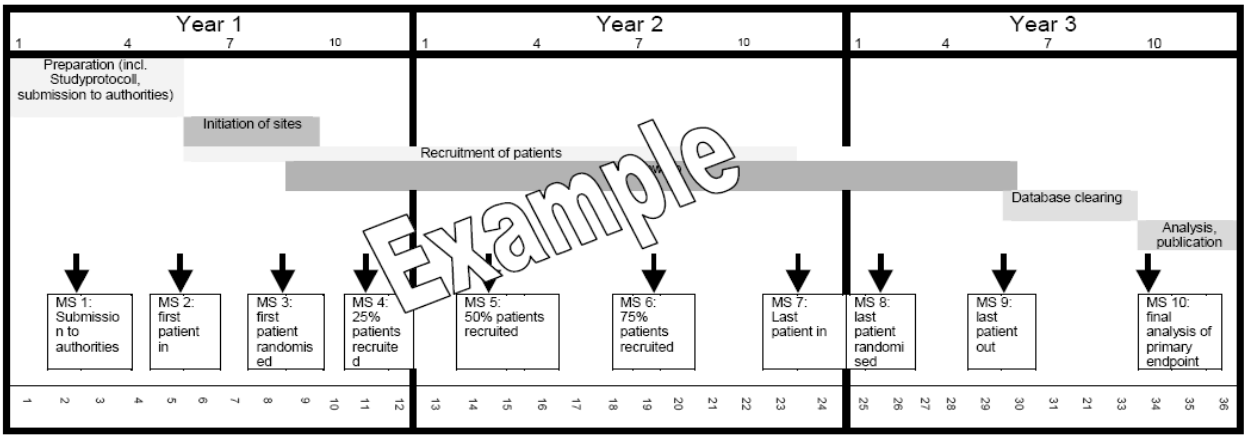
7. REFERENCES

For your references please use the Vancouver style (the full title of the publication must be displayed; please find further information here: International Committee of Medical Journal Editors.

Uniform Requirements for Manuscripts submitted to Biomedical Journals. NEJM 1997;336:309-15).

8. TRIAL TIMELINE FLOW

As funding by BMBF will critically depend on the study progression according to milestones, please provide a diagram reflecting preparation, pre-study-visits and initiation of centres, recruitment, follow-up and data cleaning/analysis. An example of such a diagram is given below.



9. LIST OF PARTICIPANTS INVOLVED IN THE TRIAL

Trial Sponsor				
Trial Management				
#	Name	Affiliation	Responsibility/Role	Signature
Trial statistician				
#	Name	Affiliation		Signature

Trial Supporting facilities *(reference laboratories, pharmacies etc.)*			
#	Name	Affiliation	Responsibility/Role

Recruiting centres *(please provide signatures on declaration of commitment)*							
#	Name	Affiliation *(only institution and city, no complete address)*	No. of patients with condition relevant to the trial seen in the last 12 months	No. of these patients fulfilling the inclusion criteria	No. of these patients which would approx. agree to participate in the trial per year	Expected no. of patients recruited for the complete trial	Source of these figures

Total sum of recruited patients					Σ =		

Data Safety and Monitoring Board (DSMB)		
#	Name	Affiliation *(only institution and city, no complete address)*

Other participating groups / bodies *(e.g. steering committee in international trials)*			
#	Name	Affiliation	Responsibility/Role

Include a tabular scientific CV (**two pages**) for the principal/ coordinating investigator. Include also tabular scientific CVs (**one page**) for academic staff members playing a leading role (i.e. co-applicants, members of the trial management, trial statistician; not all collaborating partners at all trial centres) under 11 (not separately in the appendix).
Recruiting centres must detail their commitment on a separate sheet (cf. appendix) as provided by the funding agency.
A final version of the trial protocol has to be submitted to the funding agency together with the statement by the ethics committee after the review process. While funding for a preparatory phase might be provided upon the general funding decision, funding of the actual trial can only be provided if all necessary formal and legal requirements are met.

Note: Any potential conflicts of interest must be disclosed in the appendix. The rules set forth in the "Guidelines for avoiding conflicts of interest" by the German Research Foundation (http://www.dfg.de/formulare/10_201/). These guidelines must also be considered when selecting members for the Data Safety and Monitoring Board.

10. FINANCIAL DETAILS OF THE TRIAL

Funds can only be granted for research activities. Do not include patient care costs. The tables submitted should detail resources requested clearly yet briefly.

The funds applied for should correspond to defined tasks and each task should be attributed to its respective resources. Please use the table below.
Also list tasks for which you do not request funding. In these cases, indicate the third parties which provide financial support, free services or consumables e.g. trial-related drugs and indicate their name(s) under separate headings (see also chapter 10.4).

10.1 COMMERCIAL INTEREST

Please justify, why this trial should be funded by a public funding agency and describe any potential substantial commercial interest of a single company in the results of the trial or explain why no such interest exists. Note that direct commercial interest of a single company in the results of the trial precludes funding.

10.2 FINANCIAL PLAN

Indicate total duration of the trial, the period of time for which funding is requested and when funding should begin. Funding will be granted for up to 4 years; in the case of longer trials, funding will be continued after a positive interim evaluation.

The overall expenditure should be summarized in the table below (approximately 2 pages). Indicate amounts in € in the column “Total (€)”. If duration of the total trial is longer than 4 years, indicate funds requested for years 1-4 and (if applicable) for years 5-end. Please provide man months for staff and € for all other expenditures needed in each funding period.

Please briefly justify the requested resources regarding each single task / item.

Trial stages and tasks associated with each task / item should be listed in the second column of the financial plan. You may list the individual tasks separately for each participating trial site or institute, if adequate. In the third column, please explain and justify the funds necessary for carrying out the individual tasks. Explanations given should be concise and clear to make the table easier to read. Where necessary, itemise more detailed justifications below the table, referring to the number of the individual task.

State the financial resources required of the trial in the other columns. For each individual task, indicate the man months required, using one line for each level of salary; list necessary consumables (“Sachmittel”) in a separate column.

In cases where subcontracts are foreseen, applicants should assess on a case-by-case basis whether value added tax must be considered and include this in their calculations. **Adding value added tax after the evaluation of the proposal will not be possible anymore. Thus, carefully plan subcontracts and requested funds for those now.**

Costs for tasks directly associated with the individual subject must be **detailed and justified** and pooled into a fixed rate per case, as far as reasonably possible. The individual tasks including these case payments should be highlighted (e.g. by shading the relevant lines in the table). Payment of the fixed rate per case to the participating trial centres by the principal investigator/applicant should be made in instalments. **Important: please consider that case payments may also be subject to value added tax**.

	Organizational segment / activity / task	Explanation / Comments / Items	Total				Year 1-4 (man months and €)[14]	Year 5-x (man months and €) [19]
			Staff			Consumables (€)		
			TV-L TV-Ä	Months [15]	€			
1	**Clinical Project Management**							
2	**Project Management**							
3	**Patient Involvement**	e.g. Workshops, Focus Groups, Questionnaires						
4	**Data Management**							
5	**Biometry**							
6	**Quality Assurance/ Monitoring**	number of visits per site (incl. pre-study, initiation, interim and close-out visits) mean number of days per visit (incl. preparation/ postprocessing) mean travel time per visit monitoring costs per day total no of days @ x € each						
7	**Safety / Pharmaco-vigilance**							
8	**Trial Committees**	no. of meetings @ x € / p						
9	**Meetings / Travel**	no. of meetings @ x € / p travel costs monitoring						
10	**Case Payment**	Assays / examinations per patient hours of staff per patient € / patient x no of patients						
11	**Reference Centers**	no. of samples@ x €						
12	**Materials**	Consumables, trial manuals, files, forms						

Only fill in these two columns if the trial duration exceeds 4 years

[14] Only fill in these two columns if the trial duration exceeds 4 years.

[15] Please indicate full-time equivalents

13	**Trial Drug**	€ / patient						
14	**Insurance**	€ / patient						
15	**Fees**							
16	**Equipment**	> 410 €						
17	**Publications**	Please note that only resources for open access publications will be granted						
18	**Other**							

TOTAL resources requested for the whole trial (year 1-x) € [16]	**Requested resources for years 1-4**	**Requested resources for years 5-x**
€	€	€

[16] Indicate the requested funding without overhead (“Projektpauschale”).

10.3 EQUIPMENT

Please list all requested research equipment. Explain why the equipment is essential to the project. Note that equipment commonly in use at the research institution (Grundausstattung) cannot be granted.

10.4 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.

- 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 BMBF after the review process is finished.

Please don't make any agreements before notion of award has been made; please contact the project management agency (DLR-PT) 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.

10.5 OTHER FUNDING

In case you have already submitted the same request for financial support or parts hereof to other institutions or the BMBF, 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:
"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".

11. CVs OF MAJOR PARTICIPANTS

11.1 PRINCIPAL / COORDINATING INVESTIGATOR

Include a tabular scientific CV (max. two pages) for the principal / coordinating investigator containing a list of the last five clinical trials by him/her and their reporting status with regard to registration of the trial, publication of the trial protocol and major results. Explain where trials have remained unreported.

11.2 OTHER MAJOR PARTICIPANTS

Include tabular scientific CVs (one page) for other academic staff members playing a leading role (i.e. co-applicants, members of trial management, trial statistician; not all collaborating partners at all trial centres) including a list of a maximum of 5 publications on clinical trials by him/her that have appeared during the last five years.

12. SEARCH STRATEGY

To substantiate the evidence presented in section 2.1, please present the full search strategy for one electronic database (e.g. MEDLINE, the Cochrane library or clinicaltrials.gov) including any limits used, such that it could be repeated. Indicate filters used. Present the search strategy only, do not provide further explanations. The narrative of the results is to be presented under section 2. Guidance concerning search techniques can be found here: https://www.cochrane.de/de/literaturrecherche.

Example for a full search strategy in MEDLINE (conducted to identify randomized controlled, blinded trials of antipsychotic drugs in treatment resistant patients with schizophrenia):

Search strategy for Medline (30th June 2013)

1 exp Schizophrenia/ (86112)
2 exp Psychotic Disorders/ (38267)
3 schizo$.mp. (127884)
4 or/1-3 (153641)
5 ("treatment resist$" or "therapy resist$" or "drug resist$" or "chemical resist" or "treatment refract$" or "treatment fail$" or nonrespon$ or non-respon$ or "non respon$" or "not respon$" or "no respon$" or "partial respon$" or "partially respon$" or "incomplete respon$" or "incompletely respon$" or unrespon$ or "failed to respond" or "failed to improve" or "failure to respon$" or "failure to improve" or "failed medication$" or refractory or resistant or (inadequate$ adj3 respon$)).mp. (621509)
6 exp Drug Resistance/ (253660)
7 5 or 6 (667475)
8 exp Antipsychotic Agents/ (122182)
9 antipsychoti$.mp. (50055)
10 neurolept$.mp. (20926)
11 benperidol/ or chlorpromazine/ or chlorprothixene/ or clopenthixol/ or Clopenthixol/ or clozapine/ or droperidol/ or flupenthixol/ or fluphenazine/ or fluspirilene/ or haloperidol/ or iloperidone/ or loxapine/ or mesoridazine/ or Methotrimeprazine/ or molindone/ or olanzapine/ or Penfluridol/ or Perazine/ or perphenazine/ or pimozide/ or prochlorperazine/ or promazine/ or promethazine/ or quetiapine/ or Reserpine/ or risperidone/ or sulpiride/ or thioridazine/ or thiothixene/ or trifluoperazine/ or Trifluperidol/ or triflupromazine/ or Veralipide/ or Tiapride Hydrochloride/ (69795)
12 (acetophenazine or amisulpride or aripiprazole or asenapine or benperidol or bromperidol or butaperazine or carpipramine or chlorproethazine or chlorpromazine or chlorprothixene or clocapramine or clopenthixol or clozapine or cyamemazine or dixyrazine or droperidol or fluanisone or flupehenazine or flupenthixol or fluphenazine or fluspirilene or haloperidol or iloperidone or levomepromazine or levosulpiride or loxapine or lurasidone or melperone or mesoridazine or molindone or moperone or mosapramine or olanzapine or oxypertine or paliperidone or penfluridol or perazine or pericyazine or perphenazine or pimozide or pipamperone or pipothiazine or prochlorperazine or promazine or promethazine or prothipendyl or quetiapine or remoxipiride or reserpine or risperidone or sertindole or stelazine or sulpiride or sultopride or thiopropazate or thioproperazine or thioridazine or thiothixene or tiapride or trifluoperazine or trifluperidol or triflupromazine or veralipide or ziprasidone or zotepine or zuclopenthixol).mp. (93792)
13 or/8-12 (149852)
14 4 and 7 and 13 (3026)
15 exp clinical trial/ (785982)
16 exp randomized controlled trials/ (102420)
17 exp cross-over studies/ (35635)
18 randomized controlled trial.pt. (384946)
19 clinical trial.pt. (501097)
20 controlled clinical trial.pt. (89142)
21 (clinic$ adj2 trial).mp. (597724)
22 (random$ adj5 control$ adj5 trial$).mp. (507275)
23 (crossover or cross-over).mp. (66025)
24 ((singl$ or double$ or trebl$ or tripl$) adj (blind$ or mask$)).mp. (179088)
25 randomi$.mp. (582908)
26 (random$ adj5 (assign$ or allocat$ or assort$ or reciev$)).mp. (165555)
27 or/15-26 (1088679)
28 14 and 27 (1048)

APPENDIX

In addition to the declarations of commitment of participating centers, only a list of abbreviations (max 1/2 page) and letters of support by patients or patient representatives supporting the requested trial are allowed in the appendix. These letters should best be written in English and should provide a clear and detailed statement on how and by whom the trial will be supported in its planning, conduct and result dissemination. Do not submit any other appendices (e.g. letter of intent / letter of support by other parties).

DECLARATIONS OF COMMITMENT OF PARTICIPATING CENTRES

Please use the template provided to declare the commitment of each participating centre (including the centre of the principal investigator). The template is to be signed personally by the investigator at the respective site (as named in the list of participants involved in the trail; see heading 9. of the full proposal).

Note: Only fully completed forms will be used for the assessment of recruitment feasibility in the review process. Individual estimation of recruitment figures is not regarded as a reliable source. Reported recruitment figures will be checked in case of funding (pre-study visits). In case of inconsistencies between self-assessment and checked numbers, the principal investigator will have to react appropriately and timely.

Note also that delays in patient recruitment may lead to discontinuation of funding, especially if reports from pre-study visits and monitoring visits addressing possible shortcomings were not adequately dealt with in time.

Name of investigator:
Institution:

Information on the clinical trial *(according to the full proposal)*[1]

Trial title:	
Inclusion criteria:	
Exclusion criteria:	
recruitment period (months):	

Strategy for the determination of recruitment figures

How many patients with the condition specified above have you seen in your institution during the last 12 months?	
How many of these patients would fulfil the inclusion criteria of the above mentioned trial?	
How many of these patients would approximately agree to participate in the above named clinical trial per year?	
How many patients will approximately be recruited during the entire trial?	

Which source did you use for the estimation of potential participants in the above named clinical trial?

☐ Individual estimation
☐ Hospital data management system
☐ Patient registry
☐ Others
If others: please specify

Are there any other ongoing clinical trials/ projects competing for the same patients? ☐ yes ☐ no

If yes: How will this affect recruitment for the above-named clinical trial?

Commitment to participate
I hereby agree to participate in the above-named clinical trial and support the trial by recruiting patients.

_____
Date / Signature [2]

Conflicts of Interest
I hereby declare that I have no conflict of private, economical or financial interests[3] with regard to the above mentioned clinical trial and the investigational drugs that will be used. I have no patents, whether planned, pending or issued, broadly relevant to the work.

_____
Date / Signature [2]

---

[1] Delete italic text at completion of the template.

[2] Note: This document is to be signed personally by the investigator at the respective site (as named in the list of participants involved in the trial; see 9. in the full proposal), do not submit facsimiles

[3] Any potential conflicts of interest must be disclosed in the appendix. The rules set forth in the "Guidelines for avoiding conflicts of interest" by the German Research Foundation (http://www.dfg.de/formulare/10_201/).