DLR Projektträger

Bundesministerium für Bildung und Forschung

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

Version vom 26.02.2018

Dieser Leitfaden stellt die Anforderungen für die Erstellung von beurteilungsfähigen Projektskizzen dar. Er ergänzt die am 27. Februar 2018 im Bundesanzeiger veröffentlichte o. g. Förderrichtlinie (http://www.gesundheitsforschung-bmbf.de/de/7378.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. Ansprechpartnerinnen sind:

Frau Dr. Eva Müller-Fries
Telefon: 0228-3821 1210; E-Mail: klinische-studien@dlr.de

Frau Dr. Svenja Krebs
Telefon: 0228-3821 1210; E-Mail: systematische-reviews@dlr.de

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

Entscheidungsverfahren

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 werden, werden zur Vorlage von **ausführlichen Vorhabenbeschreibungen (full proposals)** aufgefordert. Diese werden in einem zweiten fachlichen Begutachtungsschritt wiederum durch ein unabhängiges, internationales Begutachtungsgremium bewertet.

2. Projektskizzen für systematische Reviews

Für Projektskizzen für systematische Reviews ist – im Gegensatz zum Verfahren bei klinischen Studien – nur ein fachlicher Begutachtungsschritt vorgesehen. Einreichende sind zur Vorlage von **ausführlichen Vorhabenbeschreibungen (full proposals)** aufgefordert. Diese werden von einem unabhängigen, internationalen Begutachtungsgremium bewertet.

Formale Vorgaben für die Projektskizzen

Gefördert werden können:

- **Wissenschaftsinitiierte, multizentrische, prospektive, 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**, die mit geringen Probandenzahlen einen ersten Wirksamkeitsnachweis für ein Therapiekonzept liefern und der Vorbereitung von multizentrischen klinischen Studien mit hohen Probandenzahlen dienen. Mögliche Studienziele können z. B. sein:
  - die Operationalisierung der patienten-relevanten Endpunkte,
  - die Erprobung von patienten-relevanten Therapieregimen,
  - eine Nutzenabschätzung der neuen Therapie,
  - eine Dosisfindung
  - und / oder eine Abschätzung des „Benefit-Risk"-Verhältnisses.

Insbesondere klinische Studien mit Maßnahmen zur Beteiligung von Patientinnen und Patienten bzw. deren Vertretungen sollen hier gefördert werden;

- **Systematische Übersichtsarbeiten** gemäß internationaler Standards[1].

1. Projektskizzen für explorative oder konfirmatorische klinische Studien

a) Einreichen von Projektskizzen (outline proposals)

Im Sinne der Vergleichbarkeit aller eingereichten Skizzen sind die Formatvorgaben des Leitfadens verbindlich einzuhalten (s. Abschnitt „Clinical Trial Outline Application – Confirmatory Clinical Trial" bzw. „Clinical Trial Outline Application – Exploratory Clinical Trial" und der jeweilige Abschnitt „Appendices"). Bitte verwenden Sie unbedingt die aktuellen Formatvorlagen des DLR Projektträgers, die darin vorgegebene Gliederung ist verbindlich:

- http://www.dlr.de/pt/Portaldata/45/Resources/Dokumente/GF/CONFIRMATORY_CLINICAL_TRIAL_OUTLINE_APPLICATION_2018.docx
- http://www.dlr.de/pt/Portaldata/45/Resources/Dokumente/GF/EXPLORATORY_CLINICAL_TRIAL_OUTLINE_APPLICATION_2018.docx

Die Projektskizzen sind ausschließlich elektronisch als ein einzelnes pdf-Dokument einzureichen unter https://secure.pt-dlr.de/ptoutline/app/ks2018. Im Rahmen der elektronischen Einreichung wird ein pdf-Dokument zur Authentifizierung der Einreichenden generiert („Projektblatt"). **Der Ausdruck dieses Dokuments ist von folgenden Personen handschriftlich zu unterzeichnen:**

- der oder dem Haupteinreichenden **und**
- der zuständigen Biometrikerin bzw. dem zuständigen Biometriker.

Das unterzeichnete Dokument ist innerhalb von einer Woche nach Einreichungsfrist an die darauf angegebene Adresse zu senden. Es gilt das Datum des Poststempels. Die Skizzen sind zu festgelegten Terminen einzureichen, welche auf den Internetseiten des BMBF publiziert werden.

b) Einreichen von ausführlichen Vorhabenbeschreibungen (full proposals)

Einreichende, deren Skizzen im ersten Begutachtungsschritt positiv bewertet wurden, werden zur Vorlage von ausführlichen Vorhabenbeschreibungen aufgefordert. Im Sinne der Vergleichbarkeit sind dafür die Formatvorgaben des Leitfadens 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"). Bitte verwenden Sie unbedingt die aktuellen Formatvorlagen des DLR Projektträgers, die darin vorgegebene Gliederung ist verbindlich:

[1] vgl. hierzu The PRISMA statement, http://www.equator-network.org/reporting-guidelines/prisma/

- http://www.dlr.de/pt/Portaldata/45/Resources/Dokumente/GF/CONFIRMATORY_CLINICAL_TRIAL_FULL_APPLICATION_2018.docx
- http://www.dlr.de/pt/Portaldata/45/Resources/Dokumente/GF/EXPLORATORY_CLINICAL_TRIAL_FULL_APPLICATION_2018.docx

Die ausführlichen Vorhabenbeschreibungen sind ausschließlich elektronisch als pdf-Dokumente einzureichen unter https://secure.pt-dlr.de/ptoutline/app/ks2018.
Es sind zwei Dokumente vorzulegen:
(a) die ausführliche Vorhabenbeschreibung als pdf-Datei (max. 10 MB) und
(b) der Anhang als pdf-Datei (max. 30 MB).
Im Rahmen der elektronischen Einreichung wird wieder ein pdf-Dokument zur Authentifizierung der Einreichenden generiert („Projektblatt"). Das Projektblatt dient nur zu Ihrer eigenen Information und Kontrolle Ihrer Angaben. Bitte beachten Sie, dass Sie dieses Projektblatt nicht noch einmal beim DLR Projektträger einreichen müssen.

2. Projektskizzen für systematische Übersichtsarbeiten

Im Sinne der Vergleichbarkeit aller eingereichten Projektskizzen sind die Formatvorgaben des Leitfadens verbindlich einzuhalten (s. Abschnitt „Application for a Systematic Review"). Bitte verwenden Sie unbedingt die aktuelle Formatvorlage des DLR Projektträgers, die darin vorgegebene Gliederung ist verbindlich:
http://www.dlr.de/pt/Portaldata/45/Resources/Dokumente/GF/Template_Systematic_Reviews_2018.docx .
Die Projektskizzen sind ausschließlich elektronisch als ein einzelnes pdf-Dokument einzureichen unter https://secure.pt-dlr.de/ptoutline/app/ks2018. Im Rahmen der elektronischen Einreichung wird ein pdf-Dokument zur Authentifizierung der Einreichenden generiert („Projektblatt"). Der Ausdruck dieses Dokuments ist **nur** von der oder dem Projektverantwortlichen handschriftlich zu unterzeichnen und innerhalb von einer Woche nach Einreichungsfrist an die darauf angegebene Adresse zu senden. Es gilt das Datum des Poststempels. Eine Unterschrift der Biometrikerin bzw. des Biometrikers ist nicht erforderlich. Die Skizzen sind zu in den Förderrichtlinien festgelegten Terminen einzureichen, welche auf den Internetseiten der Förderer publiziert werden.

Allgemeine Hinweise

Nachfolgende Hinweise sind bei der Planung und Einreichung aller Projektskizzen und ausführlichen Vorhabenbeschreibungen 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- und PRISMA-Statements.

Zudem sind 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 .

Die Registrierung von klinischen Studien und systematischen Reviews im nationalen oder in einem internationalen Studienregister ist vorzusehen und bei Beginn der Studie nachzuweisen.

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.

Zugänglichkeit des Studienprotokolls und der Forschungsergebnisse
Um Transparenz über die durchgeführte Forschung zu erreichen, ist bei Förderung das Studienprotokoll inklusive aller Dokumentationsformulare (CRF) in einer einschlägigen Fachzeitschrift zu veröffentlichen. Die Veröffentlichung 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 Beiträge 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 6 in den Projektskizzen und Punkt 2.3 ist in den ausführlichen Vorhabenbeschreibungen der klinischen Studien zu beschreiben, wie, in welcher Verarbeitungsstufe und in welchem zeitlichen Rahmen die Forschungsergebnisse publiziert und zugänglich gemacht werden, um eine sinnvolle Nachnutzung durch Dritte zu ermöglichen (unter Wahrung der Rechte Dritter insbesondere Datenschutz, Urheberrecht). Bei Förderung müssen die Studienergebnisse innerhalb von zwei Jahren nach Schließen der Datenbank publiziert werden. In Projektskizzen für systematische Reviews ist dies analog unter Punkt 2.2 darzulegen. Die Ergebnisse eines systematischen Reviews sollten analog möglichst innerhalb von zwei Jahren nach Abschluss des Vorhabens publiziert werden.

Partizipation
Die Beteiligung und der Einbezug relevanter Akteure – allen voran von Vertreterinnen und Vertretern aus Patienten- und Bürgerschaft – erhöhen Qualität und Nutzen der Gesundheitsforschung. Deshalb sind partizipative Ansätze in der Planung, Durchführung und an der Verwertung der Ergebnisse des Vorhabens vorzunehmen bzw. einzuplanen. In besonderen Ausnahmefällen, in denen eine Einbindung nicht oder nicht in allen o. g. Projektabschritten möglich ist, sind die Gründe hierfür zu benennen. Wir verweisen in diesem Zusammenhang auf Hinweise von INVOLVE, einer Organisation, die sich im Auftrag des National Institute for Health Research im Vereinigten Königreich intensiv mit der Einbindung von Öffentlichkeit und Patientinnen bzw. Patienten in die Forschung befasst („Briefing Notes for Researchers“; http://www.invo.org.uk/resource-centre/resource-for-researchers/).

Mustervorlagen & Erläuterungen

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

Mustervorlage & Erläuterungen für Projektskizzen für konfirmatorische klinische Studien

Mustervorlage & Erläuterungen für Projektskizzen für explorative klinische Studien

Mustervorlage & Erläuterungen für ausführliche Vorhabenbeschreibungen für konfirmatorische klinische Studien

Mustervorlage & Erläuterungen für ausführliche Vorhabenbeschreibungen für explorative klinische Studien

Mustervorlage & Erläuterungen für Projektskizzen für systematische Übersichtsarbeiten

Mustervorlage & Erläuterungen für Projektskizzen für konfirmatorische klinische Studien

Clinical Trial Outline Application – Confirmatory Trial

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

To ensure comparability of all submitted outline applications please prepare your application in English **not exceeding 6 pages** (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). The number of pages includes cited literature (Only in case of a resubmission of this trial within this funding scheme, a total of 7 pages are permitted including one page with a response to previous reviewers' comments.).

Additionally two appendices are to be submitted (one page each). **Do not** submit any other appendices (e.g. letter of intent, letter of support). Structure your application using the headings listed below. Make an entry under every heading/subheading.

Signatures of the applicant and the biometrician are mandatory on the authentication sheet generated by PT-Outline ("Projektblatt").

STUDY SYNOPSIS

APPLICANT/COORDINATING INVESTIGATOR	Name, address, telephone, fax, e-mail *In case of multiple applicants the principal investigator / coordinating investigator[2] of the trial who will assume responsibility for conducting the clinical trial, should be listed first.*
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 determines sample size calculation.*
INTERVENTION(S)	*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: Follow-up per patient:

[2] 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 GCP) (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf). *1.34 Investigator: "A person responsible for the conduct of a clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator." 1.19 Coordinating investigator: "An investigator assigned the responsibility for the coordination of investigators at different centres participating in a multicenter trial."* Diese Definition sollte auch für nicht-pharmakologische Studien verwendet werden.

KEY INCLUSION AND EXCLUSION CRITERIA	Key inclusion criteria: Key exclusion criteria:
OUTCOME(S)	Primary efficacy endpoint: Key secondary endpoint(s): Assessment of safety:
STUDY TYPE	*e.g. randomized / non-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: *Please describe the strategy for assessment of safety issues in the study. Which are relevant safety variables?* 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 centers will be involved? Please also list the cities.*
PREVIOUS BMBF PROJECT NUMBER	*If applicable, the BMBF code number of the latest application or of any previous application(s) for project-funding concerning this trial.*
OTHER SUBMISSION OF PROPOSAL ELSEWHERE	*Please state, if the same or a similar version of this proposal has been submitted in another funding programme, e.g. DFG clinical trials programme.*

RESPONSE TO REVIEWERS' COMMENTS ON A PREVIOUS VERSION OF THIS TRIAL

Only for a resubmission of this trial within this specific BMBF funding scheme:
Please summarize in English the assessment of your previous application with the major recommendations given. Please respond with a short point-by-point reply separately to each recommendation (1 page max.). Where necessary, refer to changes made in this outline application.

1. RELEVANCE

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

1.1 PREVALENCE, INCIDENCE, MORTALITY

Please state the prevalence, e.g. per 100.000 residents, incidence, e. g. per 100.000 residents per year and mortality (case fatality rate) of the disease, according to most reliable data.

1.2 BURDEN OF DISEASE

Please provide suitable indicators to describe the burden of disease, e. g. DALYs (disability-adjusted life years). Please provide information on the socioeconomical burden of disease.

1.3 IMPROVEMENT OF THERAPY / IMPACT OF THE TRIAL

Novelty: Which therapy options are available for treatment of the disease? What is the novel aspect of the proposed trial? Does the trial challenge existing paradigms?

Clinical impact: Provide information on the possible impact on the delivery of health care and on clinical practice. Which evidence gap is to be closed?

Patient benefit: Describe the possible clinical / real life benefit(s) for the patients. Detail the potential impact on relieving the burden of disease and / or treatment (e.g. dose reduction, avoiding adverse effects, shortening futile treatment times).

Socioeconomic impact: Reflect on the socioeconomic impact of the trial.

1.4 PATIENT INVOLVEMENT

Please describe how patient involvement is implemented in the planning, conduct and exploitation of results of the trial[3]. Please note: Patient involvement is mandatory wherever feasible and constructive.

Who?: Which patients, patient representative(s), patients' self-help group(s) or patient advocacy group(s) 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) or patient advocacy group(s) 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) or patient advocacy group(s) 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. 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)[4] 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.

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[3] s. auch eine *Einführung von INVOLVE zugehörig zum Britischen National Institute for Health Research, NHS „Briefing note for Researchers":* http://www.invo.org.uk/resource-centre/resource-for-researchers/

[4] 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 appendix 2 (max. one page). Guidance concerning search techniques can be found in the following document:
http://www.cochrane.de/sites/cochrane.de/files/uploads/20130523_Manual_Literaturrecherche_Final.pdf.

Please note that insufficient clinical evidence precludes funding.[5]

3. JUSTIFICATION OF DESIGN ASPECTS

Please provide justifications and do not only list the respective information.

3.1 CONTROL(S) / COMPARATOR(S)

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

3.2 INCLUSION / EXCLUSION CRITERIA

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

3.3 INTERVENTION(S)

Justify the choice of your planned intervention(s). Illustrate your intervention scheme graphically in the appendix. Please consider following the TIDieR checklist and guide for describing the intervention.[6]

3.4 OUTCOME MEASURES

Justify the endpoints chosen: Are the chosen endpoints relevant for the patients? Are there other trials that have utilized this endpoint? Are there any guidelines proposing this endpoint / these endpoints? Discuss the clinical relevance of the outcome measures for the target population. Have the measures been validated?

3.5 METHODS AGAINST BIAS

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

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).

3.6 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. It is important that the sample size calculations take into account anticipated rates of non-compliance and losses to follow up.

3.7 FEASIBILITY OF RECRUITMENT

What is the evidence that the intended recruitment rate is achievable (e.g. pilot study)? Describe from what data you assessed the potential for recruiting the required number of suitable subjects. Comment on the prevalence of the disease, the access to patients and their willingness to be randomized in a trial.

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

[6] Hoffmann T, Glasziou P, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ. 2014;348:g1687

4. STATISTICAL ANALYSIS

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

5. ETHICAL CONSIDERATIONS

Discuss briefly the acceptability of the risk incurred by the individual participant versus the potential benefit for the participant / population concerned.

6. STRATEGIES FOR DATA HANDLING

Describe what measures will be implemented to ensure data management, maintenance and long-term accessibility for future reuse of your results (also by third parties, taking into account privacy rules and proprietary data). Also mention at which stage data sharing will be ensured. Please use existing standards and data repositories where appropriate.

7. TRIAL MANAGEMENT

7.1 MAJOR PARTICIPANTS

Please indicate persons responsible for design, management and analysis of the trial.

#	Name	Affiliation	Responsibility/Role
			Principal/Coordinating Investigator
			Trial Statistician [7]
			….

7.2 TRIAL EXPERTISE

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

7.3 TRIAL-SUPPORTING FACILITIES

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

8. FINANCIAL SUMMARY

Please give a rough estimation of the costs expected for the total duration of the trial.

Item	Costs (€)
Clinical Project Management	
Project Management: (e.g. Statistical Planning, Protocol, Case Report Form (CRF), Informed Consent, CRF printing)	
Case Payment	
Data management (e.g. Database Set-up and Validation Data Entry, Coding, Query Management)	
Biostatistics	
Quality Assurance (e.g. Pre-Study Visits, On-Site Monitoring, Data Monitoring and Safety Committee)	
Travel (e.g. Trial Committees, Meetings)	
Materials	

[7] Assure that the biostatistician has the expertise to carry out clinical trials, e.g.: GMDS certificate (http://www.gmds.de/organisation/zertifikate/zertifikate.php), ICH guidance E9 *"Statistical Principles of Clinical Trials".*

Trial Drug	
Fees, Insurance	
Other	
TOTAL	

Co-financing of the trial by a company:

For pharmacological interventions: trial drug under patent protection ☐ no; ☐ yes, until Date:
For interventions with medical devices: device is CE-certified ☐ no; ☐ yes

Commercial interest: 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.

References

For your references please use the Vancouver style (Further information: International Committee of Medical Journal Editors. Uniform Requirements for Manuscripts submitted to Biomedical Journals. NEJM 1997;336:309-15).

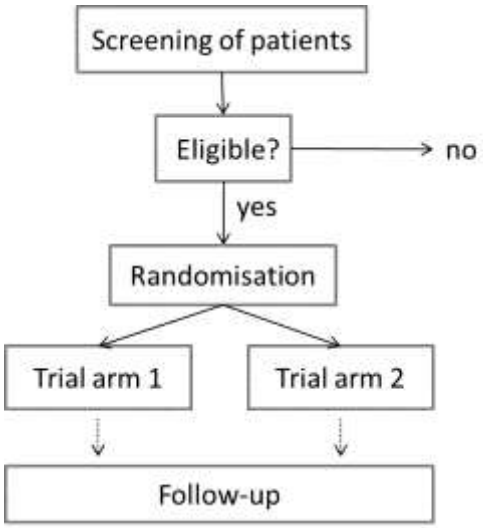
APPENDICES

The following documents (each NOT exceeding one page) have to be submitted with the outline application. Both appendices are to complement the information given in the respective sections.

1. INTERVENTION SCHEME / TRIAL FLOW

Provide a schematic diagram of the trial design illustrating the trial flow including interventions and procedures. DO NOT provide a visit schedule, procedure table, time table etc. or any other further explanations. Only abbreviations can be listed in a legend.

Basic example for a schematic diagram of the trial design:



2. SEARCH STRATEGY

To substantiate the evidence presented in section 2, 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. For guidance refer to section 3.2.5 in the document that can be accessed at http://www.cochrane.de/sites/cochrane.de/files/uploads/20130523_Manual_Literaturrecherche_Final.pdf

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)

Mustervorlage & Erläuterungen für Projektskizzen für exploratorische klinische Studien

Clinical Trial Outline Application – Exploratory Trial

To ensure comparability of all submitted outline applications please prepare your application in English **not exceeding 6 pages** (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). The number of pages includes cited literature.

Additionally two appendices are to be submitted (one page each). **Do not** submit any other appendices (e.g. letter of intent, letter of support). Structure your application using the headings listed below. Make an entry under every heading/subheading.

Signatures of the applicant and the biometrician are mandatory on the authentication sheet generated by PT-Outline ("Projektblatt").

STUDY SYNOPSIS

APPLICANT/COORDINATING INVESTIGATOR	Name, address, telephone, fax, e-mail *In case of multiple applicants the principal investigator / coordinating investigator[8] of the trial who will assume responsibility for conducting the clinical trial, should be listed first.*
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 determines sample size calculation.*
INTERVENTION(S)	*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: Follow-up per patient:
KEY INCLUSION AND EXCLUSION CRITERIA	Key inclusion criteria: Key exclusion criteria:
OUTCOME(S)	Primary efficacy endpoint:

[8] 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 GCP) (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf). *1.34 Investigator: "A person responsible for the conduct of a clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator." 1.19 Coordinating investigator: "An investigator assigned the responsibility for the coordination of investigators at different centres participating in a multicenter trial."* Diese Definition sollte auch für nicht-pharmakologische Studien verwendet werden.

	Key secondary endpoint(s): Assessment of safety:
STUDY TYPE	*e.g. randomized / non-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: *Please describe the strategy for assessment of safety issues in the study. Which are relevant safety variables?* 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): *if applicable* *How many centers will be involved? Please also list the cities.*
OTHER SUBMISSION OF PROPOSAL ELSEWHERE	*Please state, if the same or a similar version of this proposal has been submitted in another funding programme, e.g. DFG clinical trials programme.*

1. RELEVANCE

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

1.1 PREVALENCE, INCIDENCE, MORTALITY

Please state the prevalence, e.g. per 100.000 residents, incidence, e. g. per 100.000 residents per year and mortality (case fatality rate) of the disease, according to most reliable data.

1.2 BURDEN OF DISEASE

Please provide suitable indicators to describe the burden of disease, e. g. DALYs (disability-adjusted life years). Please provide information on the socioeconomical burden of disease.

1.3 IMPROVEMENT OF THERAPY / IMPACT OF THE TRIAL

Novelty: Which therapy options are available for treatment of the disease? What is the novel aspect of the proposed trial? Does the trial challenge existing paradigms?

Clinical impact: Provide information on the possible impact on the delivery of health care and on clinical practice. Which evidence gap is to be closed?

Patient benefit: Describe the possible clinical / real life benefit(s) for the patients. Detail the potential impact on relieving the burden of disease and / or treatment (e.g. dose reduction, avoiding adverse effects, shortening futile treatment times).

Socioeconomic impact: Reflect on the socioeconomic impact of the trial.

1.4 PATIENT INVOLVEMENT

Please describe how patient involvement is implemented in the planning, conduct and exploitation of results of the trial[9]. Please note: Patient involvement is mandatory wherever feasible and constructive.

Who?: Which patients, patient representative(s), patients' self-help group(s) or patient advocacy group(s) 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) or patient advocacy group(s) 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) or patient advocacy group(s) 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. EVIDENCE

Set your trial into perspective. This section should detail the background of the starting hypotheses of the trial and the need for the trial (e.g. operationalisation of a patient-relevant endpoint, feasibility of a patient-relevant therapy regimen).

How novel is the addressed question? 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.

A full electronic search strategy for one database, including any limits used, has to be presented in appendix 2 (max. one page). Guidance concerning search techniques can be found in the following document:
http://www.cochrane.de/sites/cochrane.de/files/uploads/20130523_Manual_Literaturrecherche_Final.pdf

Please note that insufficient clinical evidence precludes funding.[11]

3. JUSTIFICATION OF DESIGN ASPECTS

Please provide justifications and do not only list the respective information.

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[9] s. auch eine *Einführung von INVOLVE zugehörig zum Britischen National Institute for Health Research, NHS „Briefing note for Researchers":* http://www.invo.org.uk/resource-centre/resource-for-researchers/

[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

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

3.1 CONTROL(S) / COMPARATOR(S)

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

3.2 INCLUSION / EXCLUSION CRITERIA

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

3.3 INTERVENTION(S)

Justify the choice of your planned intervention(s). Illustrate your intervention scheme graphically in the appendix. Please consider following the TIDieR checklist and guide for describing the intervention.[12]

3.4 OUTCOME MEASURES

Justify the endpoints chosen: Are the chosen endpoints relevant for the patients? Are there other trials that have utilized this endpoint? Are there any guidelines proposing this endpoint / these endpoints? Discuss the clinical relevance of the outcome measures for the target population. Have the measures been validated?

3.5 METHODS AGAINST BIAS

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

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).

3.6 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. It is important that the sample size calculations take into account anticipated rates of non-compliance and losses to follow up.

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.

3.7 FEASIBILITY OF RECRUITMENT

What is the evidence that the intended recruitment rate is achievable (e.g. pilot study)? Describe from what data you assessed the potential for recruiting the required number of suitable subjects.

4. STATISTICAL ANALYSIS

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

[12] Hoffmann T, Glasziou P, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ. 2014;348:g1687

5. ETHICAL CONSIDERATIONS

Discuss briefly the acceptability of the risk incurred by the individual participant versus the potential benefit for the participant / population concerned.

6. STRATEGIES FOR DATA HANDLING

Describe what measures will be implemented to ensure data management, maintenance and long-term accessibility for future reuse of your results (also by third parties, taking into account privacy rules and proprietary data). Also mention at which stage data sharing will be ensured. Please use existing standards and data repositories where appropriate.

7. TRIAL MANAGEMENT

7.1 MAJOR PARTICIPANTS

Please indicate persons responsible for design, management and analysis of the trial.

#	Name	Affiliation	Responsibility/Role
			Principal/Coordinating Investigator
			Trial Statistician [13]
			….

7.2 TRIAL EXPERTISE

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

7.3 TRIAL-SUPPORTING FACILITIES

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

8. FINANCIAL SUMMARY

Please give a rough estimation of the costs expected for the total duration of the trial.

Item	**Costs (€)**
Clinical Project Management	
Project Management: (e.g. Statistical Planning, Protocol, Case Report Form (CRF), Informed Consent, CRF printing)	
Case Payment	
Data management (e.g. Database Set-up and Validation Data Entry, Coding, Query Management)	
Biostatistics	
Quality Assurance (e.g. Pre-Study Visits, On-Site Monitoring, Data Monitoring and Safety Committee)	
Travel (e.g. Trial Committees, Meetings)	
Materials	
Trial Drug	
Fees, Insurance	
Other	
TOTAL	

[13] Assure that the biostatistician has the expertise to carry out clinical trials, e.g.: GMDS certificate (http://www.gmds.de/organisation/zertifikate/zertifikate.php), ICH guidance E9 *"Statistical Principles of Clinical Trials".*

Co-financing of the trial by a company:

For pharmacological interventions: trial drug under patent protection ☐ no; ☐ yes, until Date:
For interventions with medical devices: device is CE-certified ☐ no; ☐ yes

Commercial interest: 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.

References
For your references please use the Vancouver style (Further information: International Committee of Medical Journal Editors. Uniform Requirements for Manuscripts submitted to Biomedical Journals. NEJM 1997;336:309-15).

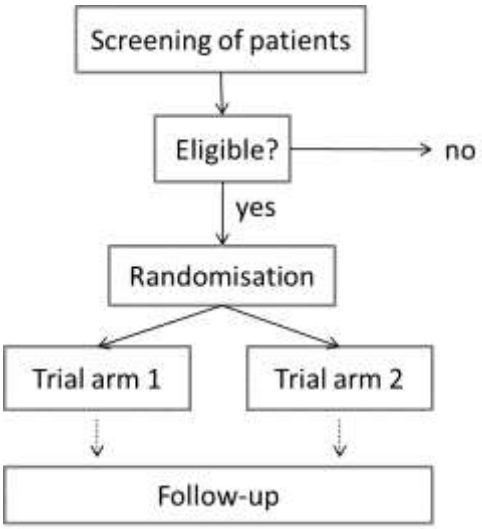
APPENDICES

The following documents (each NOT exceeding one page) have to be submitted with the outline application. Both appendices are to complement the information given in the respective sections.

1. INTERVENTION SCHEME / TRIAL FLOW

Provide a schematic diagram of the trial design illustrating the trial flow including interventions and procedures. DO NOT provide a visit schedule, procedure table, time table etc. or any other further explanations. Only abbreviations can be listed in a legend.

Basic example for a schematic diagram of the trial design:



2. SEARCH STRATEGY

To substantiate the evidence presented in section 2, 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. For guidance refer to section 3.2.5 in the document that can be accessed at http://www.cochrane.de/sites/cochrane.de/files/uploads/20130523_Manual_Literaturrecherche_Final.pdf.

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)

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2 exp Psychotic Disorders/ (38267)
3 schizo$.mp. (127884)
4 or/1-3 (153641)
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6 exp Drug Resistance/ (253660)
7 5 or 6 (667475)
8 exp Antipsychotic Agents/ (122182)
9 antipsychoti$.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)

Mustervorlage & Erläuterungen für ausführliche Vorhabenbeschreibungen 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.

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[14] 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 • Fax • 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.*
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: Follow-up per patient: Experimental and / or control off label or on label in Germany: *if applica-*

[14] 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 GCP) (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf). *1.34 Investigator: "A person responsible for the conduct of a clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator." 1.19 Coordinating investigator: "An investigator assigned the responsibility for the coordination of investigators at different centres participating in a multicenter trial."* Diese Definition sollte auch für nicht-pharmakologische Studien verwendet werden.

	ble
KEY INCLUSION AND EXCLUSION CRITERIA	Key inclusion criteria: Key exclusion criteria:
OUTCOME(S)	Primary efficacy endpoint: Key secondary endpoint(s): Assessment of safety:
STUDY TYPE	*e.g. randomized / non-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 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 KEY WORDS

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.

1.5 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)[15] 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 in the following document:
http://www.cochrane.de/sites/cochrane.de/files/uploads/20130523_Manual_Literaturrecherche_Final.pdf

Please note that insufficient clinical evidence precludes funding.[16]

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 INVOLVEMENT

Please describe how patient involvement is implemented in the planning, conduct and exploitation of results of the trial[17]. Please note: Patient involvement is mandatory wherever feasible and constructive.

Who?: Which patients, patient representative(s), patients' self-help group(s) or patient advocacy group(s) 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) or patient advocacy group(s) 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?

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[15] 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

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

[17] s. auch eine *Einführung von INVOLVE zugehörig zum Britischen National Institute for Health Research, NHS „Briefing note for Researchers":* http://www.invo.org.uk/resource-centre/resource-for-researchers/

When? When were / are patients, patient representative(s), patients' self-help group(s) or patient advocacy group(s) 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, preservation and planned retention period for the research data. Please use existing standards and data repositories where appropriate.
Discuss the dissemination of results of the trial, especially beyond regular journal publication.

3. JUSTIFICATION OF DESIGN ASPECTS

Please provide justifications. It is not sufficient to list respective parameters only.

3.1 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?

3.2 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?

3.3 ADDITIONAL TREATMENTS

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

3.4 INCLUSION / EXCLUSION CRITERIA

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

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

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

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 in the appendix.

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 end points 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.

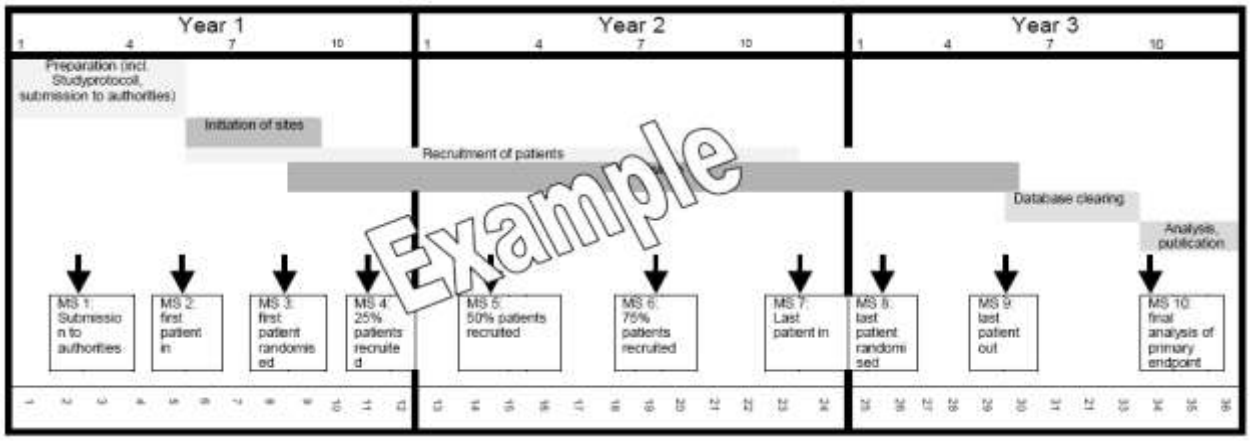
Applicants should submit their proposed arrangements for overseeing of the trial and a suggested **membership** for the committee(s). A minimum of 3 members should be listed under point 9.

7. REFERENCES

For your references please use the Vancouver style (Further information: 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. As payments by the BMBF will be made in instalments, please indicate funds needed at respective milestones.



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

Review of trial protocol *(who will review and finalize the protocol? Please refer to numbers above and/or include others)*		
#	Name	Affiliation *(only institution and city, no complete address)*

Include tabular scientific CVs (**one page**) for academic staff members playing a leading role (i.e. applicant and co-applicants, 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 no. 6) 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/).

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 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 10.5) .

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 SUMMARY

Indicate total duration of the trial, the period of time for which funding is requested and when funding should begin.
The overall expenditure should be summarized in the table below (maximum 1 page). Indicate amounts in € in the column “Total (€)”.

Keep in mind that this financial summary serves as an overview of the funds you apply for and **must not exceed 1 page**. For creation of the financial summary you must use the template table on the next page of this document.

A more detailed list of funds applied for has to be provided in the financial plan (point 10.3). This financial plan should justify in detail each item of the financial summary.

	Organizational Segment	Institution/ Participant / Trial Site	No of items/ Kind of equipment / Explanation	Qualification of staff	TV-ÖD TV-L TV-Ä	Total months	Total (€)
1	**Clinical Project Management**						
2	**Project Management**						
3	**Data Management**						
4	**Biometry**						
5	**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/ post-processing) mean travel time per visit monitoring costs per day total no of days @ x € each				
6	**Safety / Pharmaco-vigilance**						
7	**Trial Committees**	no. of DSMB members	no. of meetings @ x €/ p				
8	**Meetings / Travel**	no. of attendees	no. of meetings @ x €/ p travel costs monitoring				
9	**Case Payment**		Assays / examinations per patient hours of staff per patient € / patient x no of patients				
10	**Reference Centers**		no. of samples@ x €				
11	**Materials**		consumables				
			trial manuals, files, forms				
12	**Trial Drug**		€ / patient				
13	**Insurance**		€ / patient				
14	**Fees**						
15	**Equipment**		> 410 €				
16	**Publications**		*resources for open access publications only*				
17	**Other**						
	TOTAL						€

size of this table max. ONE page

months = staff indicated in months where applicable; € = other expenditures indicated in Euro where applicable; / p = per person

10.3 FINANCIAL PLAN

Please justify in detail the requested resources regarding each single task / item of the financial summary (10.2).

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.

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.

No.	Organizational segment / activity / task	Explanation / Comments / Items	Total ressources required			
			Staff			Consumables
			salary group	Months[1)]	€ [2)]	€ [2)]
1	**Clinical Project Management**					
2	**Project Management**					
3	**Data Management**					
4	**Biometry**					
5	**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				
6	**Safety / Pharmacovigilance**					
7	**Trial Committees**	no. of meetings @ x € / p				
8	**Meetings / Travel**	no. of meetings @ x € / p travel costs monitoring				
9	**Case Payment**	Assays / examinations per patient hours of staff per patient € / patient x no of patients				
10	**Reference Centers**	no. of samples@ x €				
11	**Materials**	Consumables, trial manuals, files, forms				
12	**Trial Drug**	€ / patient				

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

[1)] please indicate full-time equivalents
[2)] please use thousands separator

10.4 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.

10.5 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.

10.6 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

Include tabular scientific CVs (<u>one</u> page) for academic staff members playing a leading role (i.e. applicant and co-applicants, <u>not all</u> collaborating partners at all trial centres) including a list of a maximum of 5 publications by the principal / coordinating investigator that have appeared during the last five years (only the results of clinical trials).

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. For guidance refer to section 3.2.5 in the document that can be accessed at http://www.cochrane.de/sites/cochrane.de/files/uploads/20130523_Manual_Literaturrecherche_Final.pdf

APPENDIX

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). Do not submit facsimiles.

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 principle 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 Vorhabenbeschreibungen 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.

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[18] 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 • Fax • 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.*
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: Follow-up per patient: Experimental and / or control off label or on label in Germany: *if applicable*

[18] 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 GCP) (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf). *1.34 Investigator: "A person responsible for the conduct of a clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator." 1.19 Coordinating investigator: "An investigator assigned the responsibility for the coordination of investigators at different centres participating in a multicenter trial.*" Diese Definition sollte auch für nicht-pharmakologische Studien verwendet werden.

KEY INCLUSION AND EXCLUSION CRITERIA	Key inclusion criteria: Key exclusion criteria:
OUTCOME(S)	Primary efficacy endpoint: Key secondary endpoint(s): Assessment of safety:
STUDY TYPE	*e.g. randomized / non-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? *if applicable* Signed agreement to participate (n)*: How many centres have signed an agreement to participate? Full list under 9.*

1.1 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.

1.2 KEY WORDS

1.3 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.

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.

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)[19] and / or pilot studies, feasibility studies, relevant previous / ongoing trials, case reports / series. State what your study adds to the existing body of evidence.

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:
http://www.cochrane.de/sites/cochrane.de/files/uploads/20130523_Manual_Literaturrecherche_Final.pdf

Please note that insufficient clinical evidence precludes funding.[20]

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 or understanding of the proposed intervention? How will the individual patient benefit from the trial?

2.3 PATIENT INVOLVEMENT

Please describe how patient involvement is implemented in the planning, conduct and exploitation of results of the trial[21]. Please note: Patient involvement is mandatory wherever feasible and constructive.

Who?: Which patients, patient representative(s), patients' self-help group(s) or patient advocacy group(s) 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) or patient advocacy group(s) 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) or patient advocacy group(s) 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.

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[19] 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

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

[21] s. auch eine *Einführung von INVOLVE zugehörig zum Britischen National Institute for Health Research, NHS „Briefing note for Researchers":* http://www.invo.org.uk/resource-centre/resource-for-researchers/

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, preservation and planed retention period for the research data. Please use existing standards and data repositories where appropriate.

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. It is not sufficient to list respective parameters only.

3.1 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?

3.2 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?

3.3 ADDITIONAL TREATMENTS

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

3.4 INCLUSION / EXCLUSION CRITERIA

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

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

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

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?

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 in the appendix.

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 Subsequent confirmatory trial

The trial has to be directly associated to or preparation of a subsequent confirmatory trial. Therefore, please comment on the contribution of the proposed trial to the subsequent confirmatory trial and give indications about the design of the confirmatory trial and its anticipated clinical impact and relevance for the patients.

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 end points 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

6.4 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.

6.5 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).

6.6 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.

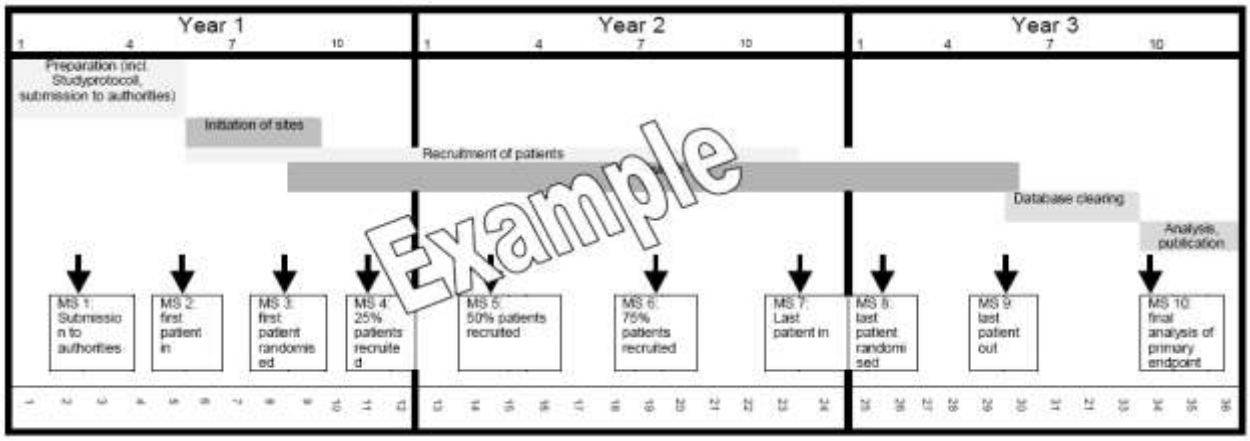
Applicants should submit their proposed arrangements for overseeing of the trial and a suggested **membership** for the committee(s). A minimum of 3 members should be listed under point 9.

7. REFERENCES

For your references please use the Vancouver style (Further information: 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. As payments by the BMBF will be made in instalments, please indicate funds needed at respective milestones.



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

Review of trial protocol *(who will review and finalize the protocol? Please refer to numbers above and/or include others)*		
#	Name	Affiliation *(only institution and city, no complete address)*

Include tabular scientific CVs (**one page**) for academic staff members playing a leading role (i.e. applicant and co-applicants, 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 no. 6) 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/).

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 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 10.5) .

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 SUMMARY

Indicate total duration of the trial, the period of time for which funding is requested and when funding should begin.
The overall expenditure should be summarized in the table below (maximum 1 page). Indicate amounts in € in the column “Total (€)”.

Keep in mind that this financial summary serves as an overview of the funds you apply for and **must not exceed 1 page**. For creation of the financial summary you must use the template table on the next page of this document.

A more detailed list of funds applied for has to be provided in the financial plan (point 10.3). This financial plan should justify in detail each item of the financial summary.

	Organizational Segment	Institution / Participant / Trial Site	No of items / Kind of equipment / Explanation	Qualification of staff	TV-ÖD TV-L TV-Ä	Total months	Total (€)
1	**Clinical Project Management**						
2	**Project Management**						
3	**Data Management**						
4	**Biometry**						
5	**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/ post-processing) mean travel time per visit monitoring costs per day total no of days @ x € each				
6	**Safety / Pharmacovigilance**						
7	**Trial Committees**	no. of DSMB members	no. of meetings @ x € / p				
8	**Meetings / Travel**	no. of attendees	no. of meetings @ x € / p travel costs monitoring				
9	**Case Payment**		Assays / examinations per patient hours of staff per patient €/patient x no of patients				
10	**Reference Centers**		no. of samples@ x €				
11	**Materials**		consumables				
			trial manuals, files, forms				
12	**Trial Drug**		€ / patient				
13	**Insurance**		€ / patient				
14	**Fees**						
15	**Equipment**		> 410 €				
16	**Publications**		*resources for <u>open access</u> publications only*				
17	**Other**						
	<u>TOTAL</u>						€

size of this table max. ONE page

months = staff inidicated in months where applicable; € = other expenditures indicated in Euro where applicable; / p = per person

10.3 FINANCIAL PLAN

Please justify in detail the requested resources regarding each single task/ item of the financial summary (10.2).

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.

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.

No.	Organizational segment/ activity/ task	Explanation/ Comments/ Items	Total ressources required			
			Staff			Consumables
			salary group	Months[1)]	€ [2)]	€ [2)]
1	**Clinical Project Management**					
2	**Project Management**					
3	**Data Management**					
4	**Biometry**					
5	**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				
6	**Safety / Pharmacovigilance**					
7	**Trial Committees**	no. of meetings @ x € / p				
8	**Meetings / Travel**	no. of meetings @ x € / p travel costs monitoring				
9	**Case Payment**	assays/examinations per patient hours of staff per patient € / patient x no of patients				
10	**Reference Centers**	no. of samples@ x €				
11	**Materials**	Consumables, trial manuals, files, forms				
12	**Trial Drug**	€ / patient				

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

[1)] please indicate full-time equivalents
[2)] please use thousands separator

10.4 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.

10.5 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.

10.6 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

Include tabular scientific CVs (one page) for academic staff members playing a leading role (i.e. applicant and co-applicants, not all collaborating partners at all trial centres) including a list of a maximum of 5 publications by the principal / coordinating investigator that have appeared during the last five years (only the results of clinical trials).

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. For guidance refer to section 3.2.5 in the document that can be accessed at http://www.cochrane.de/sites/cochrane.de/files/uploads/20130523_Manual_Literaturrecherche_Final.pdf

APPENDIX

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). Do not submit facsimiles.

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 principle 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 Projektskizzen für systematische Übersichtsarbeiten

Application for a Systematic Review

To ensure comparability of all submitted full applications, please prepare your application in English **not exceeding 13 pages** (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). The number of pages includes cited literature. Structure your application using the headings listed below. Make an entry under each heading/subheading. (Only in case of a resubmission of this systematic review within this funding scheme, 14 pages are permitted including one page with a response to previous reviewers' comments.)

A signature of the applicant is mandatory on the authentication sheet generated by PT-Outline ("Projektblatt"). A signature of the biometrician is not necessary. However, please ensure that the team of participating investigators has the necessary range of disciplines and expertise to carry out the systematic review.

SYNOPSIS

APPLICANT	*Name, address, telephone, fax, e-mail*
TITLE OF REVIEW	*The title of the review should be as precise as possible. In case of funding this title shall be quoted in the annual reports of the BMBF.*
CONDITION	*The medical condition being studied (e.g. asthma, myocardial infarction, depression)*
OBJECTIVE(S)	*Which principal research questions are to be addressed? Does the proposal aim at methodological progress in the field of reviews?*
TYPE OF REVIEW	*Key words only (e.g. IPD-analysis, prognostic review, update of an existing systematic review).*
INTERVENTION (S)	*Describe the experimental and the control interventions. For reviews on diagnostic test accuracy, index test and reference standard should appear in this section.* Experimental intervention: Control intervention:
STUDY SELECTION	*Specify key inclusion and exclusion criteria.* Population (of patients): Comparator(s): Outcomes: Design of primary studies:
SEARCH STRATEGY	*Describe the search strategy to identify relevant research, i.e. specify databases and other sources to be searched.*
QUALITY ASSESSMENT	*Describe the strategies to assess the quality of primary studies (methodological quality, systematic error, validity, generalisability, applicability).*
DATA EXTRACTION	*Specify extraction process and detail quality assessment of extracted*

	data.
DATA SYNTHESIS	*Specify strategy for data synthesis (effect measures) and presentation of results (forest plots) taking into account possible heterogeneity, publication bias and subgroup analysis.*
SAMPLE SIZE	*Estimate the number of eligible primary studies (and individual patient data, if applicable) to be included.*
COOPERATING CENTERS	
DURATION	*Requested duration of funding*
PREVIOUS BMBF PROJECT NUMBER	*If application is a resubmission, please fill in previous application number.*

KEY WORDS

RESPONSE TO REVIEWERS' COMMENTS ON A PREVIOUS VERSION OF THIS SYSTEMATIC REVIEW

Only for a resubmission of this systematic review within this funding scheme:
Please summarize in English the assessment of your previous application with the major recommendations given. Please respond with a short point-by-point reply separately to each recommendation (1 page max.). Where necessary, refer to changes made in this outline application.

1. RELEVANCE

Which medical problem is to be addressed? Which principal research questions are to be addressed? Please justify the relevance of the medical problem and the choice of the research questions.

1.1 PREVALENCE, INCIDENCE, MORTALITY

Please state the prevalence, e.g. per 100.000 residents, incidence, e. g. per 100.000 residents per year and mortality (case fatality rate) of the addressed disease, according to most reliable data. Please provide information on the socioeconomical burden of disease.

1.2 BURDEN OF DISEASE

Please provide suitable indicators to describe the burden of disease, e. g. DALYs (disability-adjusted life years).

1.3 NEED FOR THE SYSTEMATIC REVIEW

How significant is the systematic review in terms of its potential impact of relieving the burden of disease and/or burden of treatment (e.g. dose reduction, avoiding adverse effects) and/or improving quality of life?

Did you search for already existing systematic reviews in your field of interest? What is the novel aspect of the proposed systematic review in comparison to already existing reviews? Which therapy options are available for treatment of the disease? How can the systematic review influence evidence-based treatment decisions in clinical practise in Germany? How significant is the review for planning of further clinical research? Does the review contribute to methodological progress in the field of systematic reviews?

1.4 PATIENT INVOLVEMENT

Please describe how patient involvement is implemented in the planning, conduct and exploitation of results of the review[22]. Please note: Patient involvement is mandatory wherever feasible and constructive.

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

How? How have patient representative(s), patients' self-help group(s) or patient advocacy group(s) been involved in the planning of the review? 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 review and dissemination of results?

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

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

2. THE MEDICAL PROBLEM

2.1 EVIDENCE

Set your review into perspective. What research has been conducted either by you or by others? For a review update please state the present need (e.g. novel publications of clinical trials) What is the relevance of the results? Give references.

2.2 STRATEGIES FOR THE DISSEMINATION OF RESULTS

What will be your strategies for the dissemination of results? Indicate how the expected results of the systematic review will be used; discuss dissemination of results, especially beyond regular journal publication, describe intended measures, detail potential economic impact and relevance for patients' decision making. Describe what measures will be taken to ensure data management, maintenance and long-term accessibility of your results for future reuse (also by third parties). Please use existing internationally accepted standards and data repositories where appropriate.

3. JUSTIFICATION OF DESIGN ASPECTS

3.1 POPULATION

Justify the population of patients to be studied. Include reflections on generalisability and representativeness. In case of an individual patient data meta-analysis please justify feasibility of individual patient data acquisition in detail.

3.2 INTERVENTION(S)

Justify the intervention(s) to be studied. Describe the intervention(s) as exactly as possible. Address important potential adverse effects of the intervention(s).

3.3 COMPARATOR(S)

Justify the choice of comparator(s) being used by primary studies. Which evidence establishes the appropriateness of the chosen comparator(s)? Describe the control interventions as exactly as possible.

[22] s. auch eine *Einführung von INVOLVE zugehörig zum Britischen National Institute for Health Research, NHS „Briefing note for Researchers":* http://www.invo.org.uk/resource-centre/resource-for-researchers/

3.4 OUTCOMES

Justify the outcomes chosen: Are there other reviews that have utilized them? Are there any guidelines proposing them? Are they relevant for patients? Discuss the clinical relevance of the outcomes for the target population. Have they been validated? Define the timing of outcome measurements.

3.5 DESIGN OF PRIMARY STUDIES

Justify the design of the primary studies to be included/ excluded. Are there any restrictions, e.g. a minimal time of follow-up?

3.6 SEARCH STRATEGIES

Justify the search strategies to identify relevant research: Are all relevant bibliographic databases considered? Is a hand search planned? Will authors, sponsors or other experts be contacted? Present a full electronic search strategy for one bibliographic database, including any limits used, such that it could be repeated. How many eligible primary studies do you expect to be included? How did you assess their number (provide and critically evaluate published data)?

3.7 DATA EXTRACTION

Justify the data extraction strategies. Describe the tool(s) used for risk of bias assessment. Detail consequences possibly arising from quality assessment.

4. STATISTICAL ANALYSES

What is the proposed strategy of information synthesis? Will the calculation of a summary measure be justified? If yes, specify effect measures and statistical models. Describe how to investigate heterogeneity/homogeneity and publication bias based on the expected number of primary studies (sample size of your review). Are there any planned subgroup or sensitivity analyses? If applicable describe the methods for “Summary of findings” tables.

5. EXPERTISE

Please indicate persons responsible for the review.

#	Name	Affiliation	Role
			Clinical expertise
			Methodological expertise
			Cooperation partner
			….

Please indicate expertise of all above-mentioned participants by citing relevant publications and/or specifying major role in ongoing research (to be identified; max. 5 publications of the last 5 years). Ensure that the team of participating investigators has the necessary range of disciplines and expertise to carry out the systematic review (i.e. multiple treatments meta-analysis, diagnostic test accuracy review).

6. REFERENCES

For your references please use the Vancouver style (Further information: International Committee of Medical Journal Editors. Uniform Requirements for Manuscripts submitted to Biomedical Journals. NEJM 1997;336: 309-15).

7. FINANCIAL AND TIME PLAN

7.1 FINANCIAL PLAN

Please detail and justify the costs for the entire funding period.

Duration: requested duration of funding

Item			
Staff: *qualification, tasks*	*salary group*	*man months*	€
Consumables*: *detail*			€
Travel: *detail*			€
Commissions incl. tax: *detail*			€
Total			€

**Please note: Equipment cannot be funded. Publication costs can only be funded if an open access publication is planned.*

7.2 TIME PLAN

Please describe the estimated time plan considering, e.g. work packages, cooperation with the adjacent Cochrane review group, individual patient data acquisition (if applicable).