



Version vom 22.08.2011

## Programm klinische Studien Leitfaden für die Antragstellung

Die Deutsche Forschungsgemeinschaft (DFG) und das Bundesministerium für Bildung und Forschung (BMBF) haben vereinbart, im Rahmen zweier sich ergänzender und aufeinander abgestimmter Fördermaßnahmen, konfirmatorische<sup>1</sup> klinische Studien zu fördern. In beiden Maßnahmen werden die Antragstellung, die fachliche Prüfung nach international üblichen Standards und qualitätssichernde Maßnahmen einheitlich erfolgen. Insbesondere werden die Förderer einen gemeinsamen Gutachterkreis berufen. Die Randbedingungen der Förderung sind in der Förderrichtlinie des BMBF und dem vorliegenden Leitfaden niedergelegt. (Siehe auch: [www.gesundheitsforschung-bmbf.de/de/175.php](http://www.gesundheitsforschung-bmbf.de/de/175.php) und [www.dfg.de](http://www.dfg.de)).

Gefördert werden können

1. Prospektive interventionelle konfirmatorische multizentrische klinische Studien an Patienten:
  - (a) kontrollierte Therapiestudien
  - (b) kontrollierte Studien zur Sekundärprävention
  - (c) Prognose-Studien

2. Diagnosestudien der Phasen II-III<sup>2,3</sup>

3. Systematische Reviews gemäß internationalen Standards<sup>4</sup>.

Geschlechts- und altersgruppenspezifische Aspekte sind bei den Studien in angemessener Weise zu berücksichtigen.

Nicht im Rahmen des Programms gefördert werden können monozentrische Studien (nur in begründeten Ausnahmefällen), Forschungsansätze zur Rehabilitation und Versorgung Kranker sowie zu rein gesundheitsökonomischen Fragestellungen<sup>5</sup>, explorative<sup>6</sup> Studien oder Studien mit zunächst vorgeschalteten explorativen Phasen. Von der Förderung ausgenommen sind Studien, an deren Ergebnissen Unternehmen der gewerblichen Wirtschaft ein unmittelbares wirtschaftliches Interesse haben. Die beiden Förderer sind übereingekommen unterschiedliche Bereiche zu fördern.

1. Die **Deutsche Forschungsgemeinschaft** nimmt Anträge entgegen zu kontrollierten, nicht-pharmakologischen Therapiestudien sowie kontrollierten Studien zur Sekundärprävention und Prognose-Studien, sofern sie jeweils eine Intervention vorsehen, ferner Diagnosestudien.

<sup>1</sup> vgl. hierzu ICH topic E8 "General considerations for clinical trials", EMA 1997, [www.ema.europa.eu/pdfs/human/ich/029195en.pdf](http://www.ema.europa.eu/pdfs/human/ich/029195en.pdf)

<sup>2</sup> Eine Definition finden Sie unter Sackett DL and Haynes RB (2002). Evidence base of clinical diagnosis: The architecture of diagnostic research; BMJ ; 324; 539-541

<sup>3</sup> Eine Checkliste für diagnostische Studien finden Sie unter Bossyt PM et. al. (2003) Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative; BMJ; 326; 41-44

<sup>4</sup> vgl. hierzu Moher D et al., The PRISMA Group (2009) Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA statement; BMJ; 339; 332-336

<sup>5</sup> vgl. hierzu „Empfehlungen zu forschungs- und lehrförderlichen Strukturen in der Universitätsmedizin“, Wissenschaftsrat Köln, Januar 2004, S. 84-85

<sup>6</sup> siehe Fußnote 1

2. Der **Projekträger Gesundheitsforschung für das BMBF** nimmt Anträge entgegen zu kontrollierten Therapiestudien mit Arzneimitteln und zu systematischen Reviews.

Für **Anträge auf Klinische Studien** gilt ein zweistufiges Antragsverfahren. Zunächst sind Antragsskizzen einzureichen, die von einem unabhängigen Gutachterkreis geprüft werden. Antragsteller, deren Skizzen durch den Gutachterkreis positiv bewertet werden, werden zur Vorlage von vollständigen Anträgen aufgefordert.

1. Einreichen von Antragsskizzen

Die Skizzen sind nach den Vorgaben des Leitfadens (s. Abschnitt „Clinical Trial Outline Application“) zu erstellen (maximal 6-seitig incl. Literaturverzeichnis, DIN A4, in englischer Sprache). Bitte benutzen Sie die Formatvorlage auf den Internetseiten der Förderer. **Die Antragsskizzen sind ausschließlich elektronisch als PDF-Dokument einzureichen unter <http://www.pt-it.de/ptoutline/ks8/>**. Im Rahmen der elektronischen Antragstellung wird ein pdf zur Authentifizierung der Antragstellenden generiert. Der Ausdruck dieses Dokuments ist vom Hauptantragstellenden und vom zuständigen Biometriker bzw. Biometrikerin handschriftlich zu unterzeichnen und innerhalb von einer Woche nach Einreichungsfrist an die darauf angegebene Adresse zu senden. Die Skizzen sind zu festgelegten Terminen einzureichen, welche auf den Internetseiten der Förderer publiziert werden. Verspätet eingehende Skizzen können zum jeweils nächsten Einreichtermin berücksichtigt werden.

Antragsskizzen, die den Vorgaben dieses Leitfadens nicht entsprechen, können nicht berücksichtigt werden. Insbesondere führen die Überschreitung der vorgegebenen Seitenzahl und die fehlende Unterschrift des für die Studie verantwortlichen Biometrikers bzw. Biometrikerin zu einem Ausschluss aus dem weiteren Antragsverfahren.

2. Einreichen von vollständigen Anträgen

Antragsteller, deren Skizzen durch den unabhängigen Gutachterkreis positiv bewertet wurden, werden zur Vorlage von vollständigen Anträgen aufgefordert (maximal 15 Seiten für die vorgegebenen Überschriften 1. bis 8., je 2 Exemplare des Antrags und des Anhangs nach DIN A4 doppelseitig in gedruckter Form); zusätzlich sind

(a) der Antrag als pdf-Datei und

(b) der Anhang als pdf Datei sowie

(c) die Finanzübersicht (financial summary, financial plan, monitoring details) als Excel-Datei auf einer CD-ROM einzureichen.

Anträge sind entsprechend den Vorgaben dieses Leitfadens (s. Abschnitt „Full Application for the Funding of a Clinical Trial“ und Abschnitt „Appendices“) zu gliedern. Anträge, die den Vorgaben des Leitfadens nicht entsprechen, können nicht berücksichtigt werden.

Neben diesem Leitfaden gelten weiterhin die entsprechenden Merkblätter und Richtlinien der Förderer<sup>7</sup>, soweit in diesem Leitfaden nicht ausdrücklich andere Regelungen getroffen sind.

Für **Anträge auf systematische Reviews** gilt ein einstufiges Antragsverfahren, so dass direkt der ausgearbeitete Antrag eingereicht werden kann. Für die Abfassung dieser Anträge benutzen Sie bitte die Vorlage, die auf der Internetseite des Projekträgers Gesundheitsforschung [http://www.gesundheitsforschung-bmbf.de/media/Template\\_Review\\_20110826.doc](http://www.gesundheitsforschung-bmbf.de/media/Template_Review_20110826.doc) zu finden ist. Anträge, die den Vorgaben der Vorlage nicht entsprechen, können nicht berücksichtigt werden. **Die Anträge sind ausschließlich elektronisch einzureichen unter <http://www.pt-it.de/ptoutline/ks8/>**. Im Rahmen der elektronischen Antragstellung wird ein pdf zur Authentifizierung der Antragsteller/in generiert. Der Ausdruck dieses Dokuments ist vom Hauptantragsteller handschriftlich zu unterzeichnen und innerhalb von einer Woche nach Einreichungsfrist an die darauf angegebene Adresse zu senden. Die Skizzen sind zu

<sup>7</sup> DFG: Merkblatt „Sachbeihilfen“ (Nr. 1.02) (<http://www.dfg.de/forschungsfoerderung/formulare/sachbeihilfe.html>)

BMBF/Projekträger: Richtlinien für die Zuwendungsanträge auf Ausgabenbasis (AZA) des BMBF.

(<http://www.kp.dlr.de/profi/easy/bmbf/pdf/0027.pdf>). Für die wissenschaftliche Begutachtung ist in jedem Fall zunächst ein Antrag nach dem vorliegenden Leitfaden einzureichen.

festgelegten Terminen einzureichen, welche auf den Internetseiten der Förderer publiziert werden. Verspätet eingehende Skizzen können zum jeweils nächsten Einreichtermin berücksichtigt werden.

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

## Clinical Trial Outline Application

Please prepare your application in English not exceeding 6 pages (DIN A4, at least 10 point Arial and 9 point Arial for the synopsis). The number of pages includes cited literature. Make an entry under every heading/subheading. Handwritten signatures of principal/coordinating investigator and responsible biostatistician are mandatory on the confirmation of the electronic submission of the application.

Note: Applications that fail to comply with these requirements and those not providing sufficient data in section 2.1 will be rejected without peer review.

### 1. STUDY SYNOPSIS

<b>APPLICANT/COORDINATING INVESTIGATOR</b>	Name, address, telephone, fax, e-mail <i>In case of multiple applicants the principal investigator/coordinating investigator<sup>8</sup> of the trial who will assume responsibility for conducting the clinical trial, should be listed first.</i>
<b>TITLE OF STUDY</b>	<i>The title of the trial (not exceeding 140 characters) should be as precise as possible. In case of funding this title shall be quoted in the annual reports of the funding organisations. Acronym is optional.</i>
<b>CONDITION</b>	<i>The medical condition being studied (e.g. asthma, myocardial infarction, depression)</i>
<b>OBJECTIVE(S)</b>	<i>Which principal research questions are to be addressed? Specify clearly the primary hypotheses of the trial that determines sample size calculation.</i>
<b>INTERVENTION(S)</b>	<i>Description of the experimental and the control treatments or interventions as well as dose and mode of application. For diagnostic tests or procedures the index test and the reference procedure (gold-standard) should be described.</i>  <u>Experimental intervention / index test:</u>  <u>Control intervention / reference test:</u>  <u>Follow-up per patient:</u>  <u>Duration of intervention per patient:</u>
<b>KEY INCLUSION AND EXCLUSION CRITERIA</b>	<u>Key inclusion criteria:</u> <u>Key exclusion criteria:</u>
<b>OUTCOME(S)</b>	<u>Primary efficacy endpoint:</u> <u>Key secondary endpoint(s):</u> <u>Assessment of safety:</u>
<b>STUDY TYPE</b>	<i>e.g. randomized/non-randomized, type of masking (single, double, observer blind), type of controls (active/placebo), parallel group/cross-over, prognostic, diagnostic</i>

<sup>8</sup> "Investigator" as defined in the harmonised "Guideline for Good Clinical Practice" of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH GCP)(<http://www.ema.europa.eu/pdfs/human/ich/013595en.pdf>). This definition should be used accordingly for non-drug trials/studies: (1.34 Investigator) "A person responsible for the conduct of a clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator." (1.19 Coordinating investigator) "An investigator assigned the responsibility for the coordination of investigators at different centres participating in a multicenter trial."

<b>STATISTICAL ANALYSIS</b>	<u>Efficacy / test accuracy:</u> <u>Description of the primary efficacy / test accuracy analysis and population:</u> <u>Safety:</u> <u>Secondary endpoints:</u>
<b>SAMPLE SIZE</b>	<u>To be assessed for eligibility (n = ...)</u> <u>To be allocated to trial (n = ...)</u> <u>To be analysed (n = ...)</u>
<b>TRIAL DURATION</b>	<u>First patient in to last patient out (months):</u> <u>Duration of the entire trial (months):</u> <u>Recruitment period (months):</u>
<b>PARTICIPATING CENTERS</b>	<u>How many centres will be involved? (n)</u>
<b>PREVIOUS DFG/BMBF PROJECT NUMBER</b>	<i>If applicable, the DFG/BMBF code number of the latest application or of any previous application(s) for project-funding concerning <u>this trial</u>.</i>

## 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 and the feasibility of the trial. 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)<sup>9</sup> and/or (own) pilot studies, feasibility studies, relevant previous/ongoing trials, case reports/ series. State what your study adds to the totality of evidence when your study is added to previous work. Include a description of how you searched for the evidence (databases, search terms, limits) and how you assessed its quality — i.e., how you selected and how you combined the evidence. Note that missing evidence precludes funding.<sup>10</sup>

### 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 and benefit from the trial? Describe any potential commercial interest of a company in the results of the trial or explain why no such interest exists. Note that direct commercial interest of a company in the results of the trial precludes funding.

## 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? For diagnostic trials: What is the rationale for the units, cut off and/or categories?

<sup>9</sup> Eine Definition für einen systematischen Review finden Sie unter Oxman, AD (1994). Checklists for review articles, BMJ; 309; 648-51.

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

### 3.2 INCLUSION/EXCLUSION CRITERIA

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

### 3.3 OUTCOME MEASURES

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

### 3.4 METHODS AGAINST BIAS

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

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

For diagnostic trials: what is the training and expertise of persons executing and reading the index tests and the reference standards.

### 3.5 PROPOSED SAMPLE SIZE/POWER CALCULATIONS

What is the proposed sample size and what is the justification for the assumptions underlying the power calculations? Include a comprehensible, checkable description of the power calculations and sample sizes detailing the outcome measures on which these have been based for both control and experimental groups; give event rates, means and medians, 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.

### 3.6 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? What are the methods for calculating test reproducibility in diagnostic trials?

## 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. TRIAL MANAGEMENT

### 6.1 MAJOR PARTICIPANTS

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

#	Name	Affiliation	Responsibility/Role
			Principal/Coordinating Investigator
			Trial Statistician <sup>11</sup>
			....

### 6.2 TRIALS EXPERTISE

<sup>11</sup> 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"

Please indicate trials 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 range of disciplines and expertise to carry out the study.

### 6.3 TRIAL-SUPPORTING FACILITIES

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

## 7. FINANCIAL SUMMARY

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

Item	Total funding period
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. on-site Monitoring, Data Monitoring and Safety Committee)	€
Travel (e.g. Trial Committees, Meetings)	€
Materials	€
Trial Drug	€
Fees, Insurance	
Other	€
<b>TOTAL</b>	<b>€</b>

Co-financing of the trial by a company:

For pharmacological interventions: trial drug under patent protection  no;  yes, until Date.

### References

## Full Application for the Funding of a Clinical Trial

### APPLICATION FOR A GRANT TO THE FEDERAL MINISTRY OF EDUCATION AND RESEARCH (BMBF) OR THE GERMAN RESEARCH FOUNDATION (DFG)

Please indicate whether this is a new application or a continuation and indicate the requested funding period (DFG: maximum three years per application, continuation needs new application).

Please prepare your application in English **not exceeding 15 pages for the headings 1. to 8.**, including a maximum of 1 page of references. Structure your application using the headings listed below. Make an entry under every heading. Signatures of principal/coordinating investigator and responsible biostatistician are mandatory. Submit two printed versions of application and appendix (DIN A4, printed double sided, at least 10 point Arial and 9 point Arial for the synopsis); also submit as separate pdf / xls documents on one CD-ROM the

- application (as a **single** pdf-file, not exceeding 3 MB in size), the
- appendix (as **one** pdf-file), and the
- financial details (summary plan and monitoring details as xls-file).

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

#### 1. STUDY SYNOPSIS

<b>APPLICANT/COORDINATING INVESTIGATOR</b>	In case of multiple applicants the principal investigator/coordinating investigator <sup>12</sup> of the trial who will assume responsibility for conducting the clinical trial, should be listed <u>first</u> . <ul style="list-style-type: none"> <li>• First name, last name, academic title</li> <li>• Employment status</li> <li>• Date of birth, nationality</li> <li>• Institution and department (complete name)</li> <li>• Postal address</li> <li>• Telephone</li> <li>• Fax</li> <li>• E-mail address</li> <li>• Private address and telephone</li> </ul>
<b>TITLE OF STUDY</b>	<i>The title of the trial (not exceeding 140 characters) should be as precise as possible. In case of funding this title shall be quoted in the annual reports of the funding organisations. Acronym is optional.</i>
<b>CONDITION</b>	<i>The medical condition being studied (e.g. asthma, myocardial infarction, depression).</i>
<b>OBJECTIVE(S)</b>	<i>Which principal research questions are to be addressed? Specify clearly the primary hypotheses of the trial that determine sample size calculation.</i>
<b>INTERVENTION(S)</b>	<i>Description of the experimental and the control treatments or interventions as well as dose and mode of application. For diagnostic</i>

<sup>12</sup> "Investigator" as defined in the harmonised "Guideline for Good Clinical Practice" of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH GCP) (<http://www.ema.europa.eu/pdfs/human/ich/013595en.pdf>). This definition should be used accordingly for non-drug trials/studies: (1.34 Investigator) "A person responsible for the conduct of a clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator." (1.19 Coordinating investigator) "An investigator assigned the responsibility for the coordination of investigators at different centres participating in a metacentre trial."



	<p><i>tests or procedures the index test and the reference procedure (gold-standard) should be described.</i></p> <p><u>Experimental intervention / index test:</u></p> <p><u>Control intervention / reference test:</u></p> <p><u>Follow-up per patient:</u></p> <p><u>Duration of intervention per patient:</u></p> <p><u>Experimental and/or control off label or on label in Germany: <i>if applicable</i></u></p>
<b>KEY INCLUSION AND EXCLUSION CRITERIA</b>	<p><u>Key inclusion criteria:</u></p> <p><u>Key exclusion criteria:</u></p>
<b>OUTCOME(S)</b>	<p><u>Primary efficacy endpoint:</u></p> <p><u>Key secondary endpoint(s):</u></p> <p><u>Assessment of safety:</u></p>
<b>STUDY TYPE</b>	<i>e.g randomized/non-randomized, type of masking (single, double, observer blind), type of controls (active/placebo), parallel group/cross-over , prognostic, diagnostic</i>
<b>STATISTICAL ANALYSIS</b>	<p><u>Efficacy / test accuracy:</u></p> <p><u>Description of the primary efficacy / test accuracy analysis and population:</u></p> <p><u>Safety:</u></p> <p><u>Secondary endpoints:</u></p>
<b>SAMPLE SIZE</b>	<p><u>To be assessed for eligibility (n = ...)</u></p> <p><u>To be allocated to trial (n = ...)</u></p> <p><u>To be analysed (n = ...)</u></p>
<b>TRIAL DURATION</b>	<p><u>First patient in to last patient out (months):</u></p> <p><u>Duration of the entire trial (months):</u></p> <p><u>Recruitment period (months):</u></p>
<b>PARTICIPATING CENTERS</b>	<p><u>To be involved (n): <i>How many centres will be involved?</i></u></p> <p><u>Signed agreement to participate (n): <i>How many centres have signed an agreement to participate? Full list under 9.</i></u></p>
<b>PREVIOUS DFG/BMBF PROJECT NUMBER</b>	<i>If applicable, the DFG/BMBF code number of the latest application or of any previous application(s) for project-funding concerning <u>this trial</u>.</i>

### 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 two main goals: It will inform the multidisciplinary committees which make the final decision on your grant, of the principal aspects e.g. goals, design, subjects, expected outcome of your project.

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

### 1.2 KEY WORDS

### 1.3 INTERVENTION SCHEME / TRIAL FLOW

Describe the intervention scheme and give a schematic diagram (flow chart) of design, procedures and stages.

#### 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 schematic diagram.

#### 1.5 APPLICATION HISTORY

For this study, please give a short overview over the submission of previous outlines or full proposals in this programme. Which important changes have been made with regard to previous versions or in response to reviewer's comments?

### 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; substantiate your starting hypothesis. What is the rationale for the intervention? 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)<sup>13</sup> and/or (own) pilot studies, feasibility studies, relevant previous/ongoing trials, case reports/series. State what your study adds to the totality of evidence when your study is added to previous work. Include a description of how you searched for the evidence (databases, search terms, limits) and how you assessed its quality — i.e., how you selected and how you combined the evidence. Note that missing evidence precludes funding.<sup>14</sup>

#### 2.2 THE NEED FOR A TRIAL

What impact will the results have on clinical practice or understanding of the proposed intervention or underlying disease? Why is a trial needed now?

How will a) the individual patient and b) society/science benefit from the trial? Detail potential economic impact.

#### 2.3 STRATEGIES FOR DATA HANDLING AND THE DISSEMINATION OF RESULTS

Describe what measures will be implemented to ensure the data management, curation and long-term preservation for future reuse. Please regard existing standards and data repositories where appropriate. What will be your strategies for the dissemination of results? Indicate how the expected results of the trial will be used; discuss dissemination of results, especially beyond regular journal publication, describe intended measures.

### 3. JUSTIFICATION OF DESIGN ASPECTS

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

#### 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? For diagnostic trials: What is the rationale for the units, cut off and/or categories?

#### 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 diagnostic trials: What is the rationale for the units, cut off and/or categories?

#### 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.

<sup>13</sup> Eine Definition für einen systematischen Review finden Sie unter Oxman, AD (1994). Checklists for review articles, BMJ; 309; 648-651.

<sup>14</sup> vgl. hierzu Clark S and Horton R (2010). Putting research into context – revisited; The Lancet; 376(9734); 10-11

### 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? Discuss the clinical relevance of the outcome measures for the target population. Have the measures been validated? Justify appropriateness and limitations of composite endpoints, if applicable.

#### **Determination of primary and secondary measures**

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

### 3.6 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).

For diagnostic trials: what is the training and expertise of persons executing and reading the index tests and the reference standards.

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

#### **Compliance/Rate of loss to follow up**

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

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

### 3.8 FEASIBILITY OF RECRUITMENT

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

#### a) Pilot study

Has any pilot study been carried out using this design?

#### b) Achievability of recruitment rate

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

#### **International collaborations**

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

appendix. Please detail the power of the German component of the trial on its own as well as part of the international study.

### 3.9 STOPPING RULES

Please specify the “stopping rules” or “discontinuation criteria” a) for the individual patient and b) for the whole trial. Please specify rules for closing participating centers, which fail to include the estimated number of patients.

## 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? What are the methods for calculating test reproducibility in diagnostic trials?

## 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 AND SAFETY

### 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 agencies will insist on the conduct of pre-trial visits before trial starts in each recruiting centre by independent bodies. Please make sure to include these as a milestone into the time plan and into the budget. The results of these visits should be documented and reported back to the funding agency. Note that insufficient results of pre-study visits may lead to discontinuation of funding.***

### 6.2 SAFETY

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

*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 institution involved. This will normally take the form of a scientific advisory board/trial steering committee (TSC) and/or an independent data monitoring and safety committee (DSMB).*

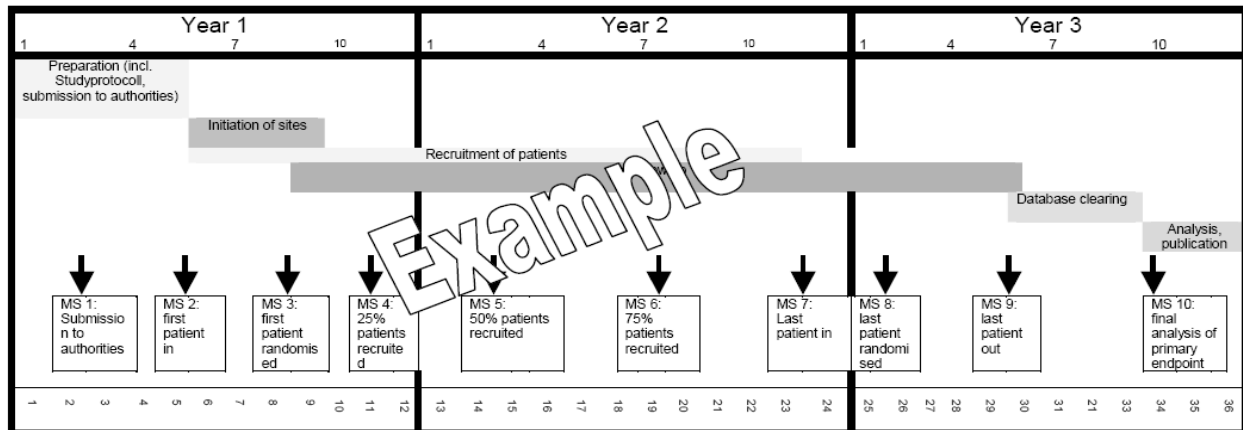
*It is recognised that these arrangements may not always be appropriate and the committees needed may vary according to the nature of the study. Thus, the arrangements for supervision should be detailed and justified. The role of these committees can comprise to monitor and supervise the progress of 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 organisations 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 named. List under 9.*

## 7. REFERENCES

## 8. TRIAL TIMELINE FLOW

As funding by BMBF/DFG will critically depend on the study progression according to milestones, please provide a diagram reflecting preparation, initiation of centres, recruitment, follow-up and data cleaning/analysis. An example of such a diagram is given below. As payments by the funding organizations 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 ( <i>central laboratories, pharmacies etc.</i> )				
#	Name	Affiliation	Responsibility/Role	
Recruiting centres ( <i>please provide signatures on declaration of commitment</i> )				
#	Name	Affiliation ( <i>only institution and city, no complete address</i> )	Expected no. of patients recruited for the complete trial	

<b>Total sum of recruited patients</b>		$\Sigma =$
<b>Data Monitoring and Safety Board (DMSB)</b>		
#	Name	Affiliation ( <i>only institution and city, no complete address</i> )

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

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

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 organization 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 the review process" by the DFG have to be observed ([http://www.dfg.de/forschungsfoerderung/formulare/download/10\\_20.pdf](http://www.dfg.de/forschungsfoerderung/formulare/download/10_20.pdf)).

## 10. FINANCIAL DETAILS OF THE TRIAL

### 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 commercial interest of a 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. Funding by the DFG is granted for up to 3 years; in the case of longer trials a continuation application will be necessary. Funding by BMBF may be granted for the total period necessary to conduct the trial.

The overall expenditure should be summarized in the table below (maximum 1 page). Indicate amounts in € in the column "Total (€)". For years 1-3 and 4-end please provide man months for staff and € for all other expenditures.

	Organizational Segment	Institution/ Participant/ Trial Site	No of items/ Kind of equipment/ Explanation	Qualification of staff	BAT	Total months	Total (€)	y1 – y3 (months/€)	y4 - yx (m/€)
1	Clinical project management								
2	Project management								
3	Data Management								
4	Biometry								
5	Quality Assurance/ Monitoring		number of visits per site mean number of days per visit monitoring costs per day total no of visits @ x € each						
6	Trial committees	no. of DSMB members	no. of meetings @ x €/p						
7	Meetings/ Travel	no. of attendees	no. of meetings @ x €/p travel costs monitoring						
8	Case payment		assays/examinations per patient hours of staff per patient €/patient x no of patients						
9	Reference centers		no. of samples @ x €						
10	Materials		consumables trial manuals, files, forms						
11	Trial drug		€/patient						
12	Insurance		€/patient						
13	Fees								
14	Publications								
15	Equipment		< 10.000 € > 10.000 € > 50.000 €						
16	Other								
<b>TOTAL</b>							€	€	€

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

### 10.3 FINANCIAL PLAN

**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 its respective resources. Please use the table below.

Also list tasks for which you do not request funding. In these cases, indicate the third parties which provide financial support, free services or consumables e.g. trial-related drugs and indicate their name(s) under separate headings (see also chapter 10.5).

Trial stages and tasks associated 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. As a rule, 40% of the amount should be paid on recruitment, another 40% when the case report form has been received by the documentation centre and the remaining 20% should be paid after all queries have been answered. The payment modalities envisaged should be stated in the application.

No.	Organizational segment/ activity/ task	Explanation/ Comments/ Items	Total resources required (DFG: years 1-3 only, further resources subject to reapplication)			
			Staff			Con- sumables
			salary group	Months <sup>1)</sup>	€ <sup>2)</sup>	€ <sup>2)</sup>
1						
2						
3						
<b>TOTAL</b>						
<b>TOTAL RESOURCES APPLIED FOR</b>						

<sup>1)</sup> please indicate full-time equivalents

<sup>2)</sup> please use thousands separator

### 10.4 EQUIPMENT

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



**Scientific instrumentation**

Scientific instrumentation may require installation and running costs, such as refurbishments in the building, additional laboratory expenses, working materials, maintenance costs and operating staff. These expenses cannot be covered by DFG or BMBF funding. Applicants must ensure that such costs are provided by their institution before sending in their project.<sup>15</sup>

**Application of instrumentation of more than 10.000 €**

Please list all requested *instrumentation which costs more than 10.000,- EUR* per item (sales price including taxes and other) with details and price information as follows. Please mark the relevant items in the offers which you enclose:

Instrument A (type)

Offer by ..... of ..... EUR

Company ..... date .....

Accessories

(listed separately by brief reference. Mark the relevant items in the offer)

Instrument B

.....

.....

.....

Cost of purchase ..... **EUR**

Please explain why this instrumentation is essential to the project and justify its necessity in relation to the core support furnished by the institution. Requested instrumentation must be described in sufficient detail (i.e. technical specification) to assure that the capabilities meet the requirements described in the work programme (e.g. measuring field, resolution, sensitivity). In addition, please justify the need for the accessories as requested. The technical specification of instrumentation should be stated precisely.

Please state the total period of instrumentation use in the scope of the research project you are planning and - where applicable - possible use by other scientists.

Please make inquiries about the prices of requested instrumentation that fulfil the necessary specifications. The models which you favour should be compared concerning their suitability for the project by naming the producing company, the type of accessories, performance and prices. Please submit relevant comparable offers. Your preference should be explained in detail, especially if there is only one model that you regard as suitable for your purpose. In addition to the technical data and the price, other conditions such as the availability of equipment in the university area, your experience with comparable instruments, the exchange of measuring programmes, the possibility of technical maintenance and similar reasons may play a role. If the choice of equipment is not explained in detail, the selection will be based solely upon price criteria.

All requested *instrumentation that costs less than 10.000,- EUR* per item should also be listed in a form as above, naming different types and price and including an explanation as to why this equipment is necessary.

<sup>15</sup> For applications to the DFG, please consider the following: Unless the grant letter specifies other arrangements, all scientific instruments provided which exceed a total individual cost (including V.A.T. and delivery costs) of more than 10.000,- EUR will be purchased by the DFG and provided on loan to the grant holder for the duration of the project. Smaller instruments are usually purchased by the grant holder. If he or she works in a public institution, the instrumentation will become the property of the institution and must be registered in its inventory at the time of delivery. The grant holder has the right to use the equipment for the duration of the research project.

In special cases smaller instruments remain DFG property and are provided to the grant holder on loan for the duration of the project. Examples are accessories and additions to DFG-owned instruments or instruments which are required for a short time and may be redeployed elsewhere, or in cases where the grant holder will change his/her institutional affiliation. Details will be specified in the grant letter.

**Application of instrumentation of more than 50.000 €**

If you request *instrumentation with a purchase price of more than 50.000,- EUR*, a formal statement is expected that the maintenance/running costs and the installation have been clarified with your host institution prior to the application.

If existing instrumentation required for your project is only accessible to you by paying a fee, please quote these costs and give details.

**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 funding organizations after the review process is finished.

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

**10.6 OTHER FUNDING**

In case you have already submitted the same request for financial support or parts hereof to other institutions or to the DFG 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/the German Research Foundation 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. 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 trial; see heading 9. of the full proposal). Do not submit facsimiles.

Name of investigator:

Institution:

### Information on the clinical trial (according to the full proposal)<sup>1</sup>

<u>Trial title:</u>	
<u>Inclusion criteria:</u>	
<u>Exclusion criteria:</u>	
<u>recruitment period (months):</u>	

### 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<sup>2</sup>

### Conflicts of Interest

I hereby declare that I have no conflict of private, economical or financial interests<sup>3</sup> with regard to the above mentioned clinical trial and the investigational drugs that will be used.

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Date/ Signature <sup>2</sup>

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<sup>1</sup> Delete italic text at completion of the template.

<sup>2</sup> 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

<sup>3</sup> Any potential conflicts of interest must be disclosed. The rules set forth in the "Guidelines for the review process" by the DFG have to be observed ([http://www.dfg.de/forschungsfoerderung/formulare/download/10\\_20.pdf](http://www.dfg.de/forschungsfoerderung/formulare/download/10_20.pdf)).

## APPENDICES

Documents specified under appendix headings 1. to 5. have to be submitted **with** the application. Documents 6. to 8. may be submitted later but are mandatory before trial funding can start.

### 1. STAFF AND INSTITUTION'S CONTRIBUTION (GRUNDAUSSTATTUNG)

Please indicate name, academic titles and employment grade of participating scientists and the number of technical employees who - without being paid through the funding applied for - will be working on the project. Please list separately the persons paid by the institution's basic funding and those paid from other grants.

Please state the annual fund for consumables which comes from the institution's budget or any other third party (please list separately) to pay for the research for which your project is part of. Use estimates where applicable.

### 2. SUPPORTING INFRASTRUCTURE OF THE MEDICAL INSTITUTION(S)

The funding organisations expect appropriate participation by the institution(s). Please indicate the resources available at your medical institution:

- existing trial-specific supporting facilities
- previous experience with the conduct of clinical trials in accordance with GCP
- possibilities for the training of trial staff
- opportunities for earning a doctorate or qualifying as a professor with scientific achievements gained in clinical trials
- consideration of clinical trials in the performance-related allocation of research resources (leistungsorientierte Mittelvergabe)

### 3. "VERTRAUENSDOZENT" (ONLY FOR APPLICATIONS TO THE DEUTSCHE FORSCHUNGSGEMEINSCHAFT)

If you belong to a university who is member of the DFG you should inform the Vertrauensdozent of your university about this application and mention this here.

### 4. DECLARATION OF CONFLICTS OF INTEREST

Any potential conflicts of interest must be disclosed (see and use template for "Declaration of Commitment of Participating Centres under heading 6. in the appendix). The rules set forth in the "Guidelines for the review process" by the DFG have to be observed ([http://www.dfg.de/download/formulare/10\\_201\\_e/10\\_201e.pdf](http://www.dfg.de/download/formulare/10_201_e/10_201e.pdf)).

### 5. MONITORING DETAILS

Duration of the entire trial		years
Number of patients to be allocated to trial		
Mean number of patients / site		
Participating sites (n)		
Total monitoring costs		€
One site visits		
Preparation and postprocessing		
Travel		
Monitoring costs / patient		
Monitoring costs (staff) / day		€
Total number of visits per site (n)		
Duration of initiation visit / site		days
Duration of interim visits / site		days
Duration of close-out visit / site		days
Mean travel time / visit		days
Preparation and postprocessing / visit		days

## **6. REGISTRATION**

PLEASE NOTE that the Deutsche Forschungsgemeinschaft and the Federal Ministry of Education and Research support the initiative of the European Science Foundation to achieve Europe-wide registration of all randomized controlled clinical trials in the long term. Therefore all randomized controlled trials should be registered immediately on receipt of the notification of award at registry that is searchable by the public at no charge (as the *German Clinical Trials Register* (<http://www.germanctr.de/>) or *Current Controlled Trials*). The registration is mandatory for funding and may be submitted later than the full proposal.

## **7. SPONSOR'S DECLARATION**

The sponsor's declaration is later mandatory for funding and may be submitted later than the full proposal.

*The medical institution receiving the funds by the DFG or the BMBF has the responsibility to ensure that the clinical trial is conducted according to the highest standards regarding the safety of subjects and the quality of data.*

*It is expected that the persons responsible in the respective institution are aware of the trial run through their department(s) and must ensure to provide the principal/coordinating investigator with support required. Any problems associated with the trial should be jointly resolved by the institution and the principal/coordinating investigator without delay. The awarding of funds is therefore linked to the condition that the medical institution employing the principal/coordinating investigator assumes full responsibility and all functions and obligations of the sponsor as listed in chapter 5 of the harmonised "Guideline for Good Clinical Practice" of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH GCP)<sup>16</sup>, notwithstanding the fact that the funding organisation provides additional external funds.*

In particular, appropriate agreements should be concluded with the parties conducting the trial in order to ensure that the responsibility referred to above can be exercised. A corresponding declaration has therefore to be submitted comprising the assurance that the trial will be conducted in accordance with the principles of ICH GCP and the medical institution will assume the sponsor's responsibilities in accordance with chapter 5 of ICH GCP.

The text of the sponsor's declaration is available on the funding organisations' web sites. Please use this text for your declaration, which must be duly signed by a representative of the medical institution and the principal/coordinating investigator.

## **8. APPROVAL OF THE RESPONSIBLE ETHICS COMMITTEE**

Please submit the approval / favourable opinion of the responsible ethics committee's review of the trial as soon as possible. This approval is mandatory before funding of work with patients can start.

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<sup>16</sup> <http://www.ema.europa.eu/pdfs/human/ich/013595en.pdf>