



Leitfaden für die Antragstellung im Rahmen der Fördermaßnahme „Molekulare Diagnostik“

Dieser Leitfaden stellt die Anforderung an die Gestaltung eines begutachtungsfähigen Antrags detailliert dar und ergänzt die [Förderrichtlinie des BMBF](#). **Anträge, die den Vorgaben der Förderrichtlinie und des Leitfadens nicht entsprechen, können ohne weitere Prüfung abgelehnt werden.**

Für weitere Fragen steht der vom BMBF beauftragte Projektträger Gesundheitsforschung im PT-DLR zur Verfügung.

Im Rahmen der Fördermaßnahme 'Molekulare Diagnostik' stellt das BMBF Fördermittel zur Verfügung, die für die Validierung von aus der Grundlagenforschung abzuleitenden Kandidaten für innovative Biomarker im Bereich der präklinischen Forschung ab dem proof of principle (ggf. im Tiermodell) bis einschließlich diagnostischer Studien der Phase III¹ beantragt werden können. Die Einbindung industrieller Partner ist wünschenswert.

Spezifische Hinweise zur Förderung:

- Diese Ausschreibung hat einen ausschließlichen Fokus auf der **Validierung** (nicht der Identifizierung) **von Biomarkern**. Innovationen sind hier als die Translation vorhergehender Resultate in die Validierung und Anwendung mit eindeutigem diagnostischen/therapeutischen/prognostischen Nutzungspotential zu verstehen. In einer geplanten Translation müssen die jeweils erforderlichen Experten (Kliniker, Technologie- und Statistikexperten) überzeugend eingebunden sein.
- Der Mehrwert der beantragten neuen Methode/des beantragten neuen Ansatzes muss erläutert werden, einschließlich der Nennung des relevanten ‚Gold Standard‘ oder des/r etablierten diagnostischen Verfahrens/Methode, gegen das/die verglichen werden soll und einer adäquaten biometrischen Ist/Soll-Analyse.
- Hierzu müssen die Anträge den beabsichtigten Ansatz in der (prä)klinischen Situation eindeutig erklären und Meilensteine für jedes Subprojekt definieren. Dazu gehört auch die Risikoanalyse zur Erreichung der Meilensteine einschließlich der Nennung möglicher Hemmnisse.

¹ Nach Sackett DL, Haynes RB *The architecture of diagnostic research. BMJ 2002, 324: 539 - 541*

- Eine Assayentwicklung kann nur beantragt werden, sofern sie für die Validierung der vorgesehenen Biomarker erforderlich ist.
- Namen und Art der zu validierenden Biomarker müssen genannt werden.
- Anträge müssen die relevante Patent/Lizenzsituation, einschließlich methodologischer Aspekte erläutern (siehe auch Risikoanalyse) und den ‚freedom to operate‘ darlegen. D. h. Klärung der Frage, ob die Validierung und spätere Verwertung der Ergebnisse durch mögliche anderweitige Schutzrechte für sowohl Ziel- als auch Markermoleküle, die Methode oder das/die Reagenz/ien tangiert wird.

Allgemeine Hinweise zur Förderung:

- In der Fördermaßnahme können **Forschungsverbände mit in der Regel 3-5 Partnern** gefördert werden. Ein Projektpartner ist jede im Verbund eingebundene Arbeitsgruppe an einer bestimmten Institution, welche ein oder mehrere Arbeitspakete innerhalb des Gesamtprojekts bearbeitet.
- Die **Projektförderung von Forschungseinrichtungen, die gemeinsam von Bund und Ländern grundfinanziert werden** (d.h. Helmholtz-Zentren sowie Einrichtungen der Max-Planck-Gesellschaft und der Wilhelm-Gottfried-Leibniz-Gemeinschaft), ist nur im Rahmen einer Zusatzfinanzierung für ihren zusätzlichen Aufwand möglich. Eine Einbindung der Forschungseinrichtung in ein Verbundvorhaben muss im Hinblick auf die Bereitstellung ihrer spezifischen Expertise und Know-how für die Durchführung des Gesamtprojektes unbedingt notwendig sein. Hierbei handelt es sich um bestimmte zeitlich befristete projektspezifische Aufgaben, die im Rahmen der Grundfinanzierung der Institution nicht durchgeführt werden können.
- **Bonität:**
Unternehmen der gewerblichen Wirtschaft können nur dann gefördert werden, wenn die Bonität des Unternehmens für die beantragte Laufzeit der Fördermaßnahme gesichert ist. Der Förderer behält sich daher vor, geeignete Unterlagen (z.B. testierte Jahresabschlüsse, Lageberichte, Betriebswirtschaftliche Auswertung) in der zweiten Verfahrenstufe bei Vorlage des förmlichen Förderantrages anzufordern, durch die nachzuweisen ist, dass die in den Vorhaben aufgeführten Ressourcen der Antragsteller für die gesamte Laufzeit der Förderung aufgebracht werden können.
- **Unternehmen der gewerblichen Wirtschaft können i.d.R.** - je nach Anwendungsnähe des Vorhabens - bis zu 50% vom BMBF anteilfinanziert werden.
 - Bei KMU² kann über die oben genannten Förderquoten hinaus noch eine Erhöhung der Förderquote um **10%** (KMU-Bonus) und um weitere **10%** gewährt werden, wenn es sich um eine „wirkliche“ Zusammenarbeit zwischen KMU und öffentlicher Hochschule/Forschungseinrichtung handelt (Verbundbonus).
 - Die Einbindung ausländischer Partner in ein Verbundvorhaben ist möglich, sofern deren Kompetenz für den Erfolg des Gesamtprojektes entscheidend ist und ein hoher Anteil an der Wertschöpfungskette in Deutschland erfolgt. Die Finanzierung des ausländischen Teilprojektes muss entweder durch andere Geldgeber gesichert sein oder der Partner per Auftragsvergabe eingebunden werden. Für deutsche Partner kann ein Bonus von **10%** gewährt werden, wenn das Projekt im Rahmen einer „wirklichen“ grenzüberschreitenden Zusammenarbeit (keine Auftragsvergabe) zwischen mindestens zwei unabhängigen Partnern

²Kleine und mittlere Unternehmen im Sinne der Definition der Europäischen Kommission (http://ec.europa.eu/enterprise/policies/sme/facts-figures-analysis/sme-definition/index_en.htm). Das bedeutet, dass die Unternehmen weniger als 250 Beschäftigte, einen Jahresumsatz von höchstens 50 Mio. EUR oder eine Jahresbilanzsumme von höchstens 43 Mio. EUR haben und nicht zu 25% oder mehr des Kapitals oder der Stimmanteile im Besitz von Unternehmen sind, welche die KMU-Kriterien nicht erfüllen.

aus anderen EU-Mitgliedsstaaten durchgeführt wird. Dieser Bonus kann nicht mit dem o.g. Verbundbonus kombiniert werden.

- Die Boni können nur bis zu maximal **20%** kumuliert werden.
- **Diagnostische Studien:**
 - Falls die Durchführung einer klinisch/diagnostischen Studie beantragt wird, soll vorab mit dem zuständigen Projektträger (siehe unten) Kontakt zur Beratung aufgenommen werden.
 - Bei Beantragung einer klinisch/diagnostischen Studie sind die unter Punkt B „Diagnostic study outline application“ der „Guideline for Project Application“ aufgeführten Angaben essentiell.
 - Im Falle einer positiven Begutachtung muss dem Förderer vor Beginn der Patientenrekrutierung das uneingeschränkt positive Ethikvotum (und die dem Ethikvotum zugrunde liegende Version des Studienprotokolls), die rechtsverbindlich unterzeichnete Verpflichtung auf die Leitlinie zur Guten Klinischen Praxis (ICG-GCP), eine Erklärung aller Mitglieder des unabhängigen Datenüberwachungskomitees (DSMC) sowie eine Bestätigung über die erfolgte Registrierung der Studie im „Deutschen Register Klinischer Studien“ (http://www.germanctr.de/index_de.html) vorgelegt werden.

HINWEISE ZUR ANTRAGSTELLUNG:

Projektanträge können bis spätestens **07.10.2010** eingereicht werden. Die Vorlagefrist gilt nicht als Ausschlussfrist. Verspätet eingehende Vorhabenbeschreibungen können aber möglicherweise nicht mehr berücksichtigt werden. Bei verspäteter Einreichung wird dringend die vorherige Kontaktaufnahme mit dem zuständigen Projektträger empfohlen. Eine Vorlage per Email oder FAX ist nicht möglich. Aus der Vorlage einer Vorhabenbeschreibung kann kein Rechtsanspruch auf Förderung abgeleitet werden.

Ein Projektantrag besteht aus zwei Teilen:

- A) der **Vorhabenübersicht** (Kontakt und Finanzdaten, Kurzbeschreibungen), die über ein Internetformular vorgelegt werden
- B) der **Vorhabenbeschreibung** als PDF Dokument

Beide Teile sind durch den Verbundkoordinator elektronisch über ein [Internet-Portal](#) einzureichen.

Vorgehen:

1. Der Verbundkoordinator stellt zur Antragstellung zunächst folgende Unterlagen als **EIN** PDF-Dokument zusammen (bitte beachten Sie das Größenlimit von 3Mb):
 - die Vorhabenbeschreibungen des Forschungsverbundes und der Teilprojekte nach den Vorgaben dieses Leitfadens (Format: DIN A4, 11 Punkt Arial, 1,5-zeilig, doppelseitig) in **englischer Sprache**.
2. Das Einreichen des Antrags erfolgt über das [Internet-Portal](#) durch den Verbundkoordinator.
3. Zunächst werden die erbetenen Übersichtsangaben und der Finanzplan inkl. der Teilprojekte zum Vorhaben in das Internetformular eingetragen (Teil A - Vorhabenübersicht).
4. Nachdem alle Daten in die vorgegebenen Felder eingetragen sind, können diese über die Vorschaufunktion unter dem Menüpunkt „Kontrolle und Abgabe“ überprüft werden.
5. Anschließend kann unter dem Menüpunkt „Kontrolle und Abgabe“ die Vorhabenbeschreibung (s. Punkt 1) als PDF-Dokument hochgeladen werden. **HINWEIS:** Es kann nur ein einziges PDF Dokument hochgeladen werden. Mit dem Hochladen weiterer Dokumente werden automatisch alle früheren PDF-Dokumente überschrieben.

6. Ebenfalls unter dem Menüpunkt „Kontrolle und Abgabe“ werden abschließend beide Antragsteile verbindlich eingereicht („Button: Antrag jetzt verbindlich einreichen“). Diese elektronische Version ist die Grundlage der Begutachtung.
7. Nach dem verbindlichen Einreichen des Antrags sind die im Internet verfügbaren Versionen der Vorhabenübersicht und der Vorhabenbeschreibung auszudrucken. Die Vorhabenübersicht darf nicht mehr den Aufdruck „Preview“ tragen.

Ihren Antrag (Vorhabenübersicht und Vorhabenbeschreibung) können Sie bis spätestens **07.10.2010**, elektronisch einreichen. Damit die Online-Version Bestandskraft erlangt, muss der Antrag in Papierform (s. Punkt 7) doppelseitig, gebunden in 5-facher Kopienzahl + eine Kopiervorlage mit den Unterschriften des Verbundkoordinators und des Biostatistikers beim

Projektträger im DLR für das BMBF
Gesundheitsforschung
Heinrich-Konen-Str. 1
53227 Bonn

eingereicht werden.

Eine Vorlage per Email oder Fax ist nicht möglich. Als Hilfestellung für die Antragstellung ist die unten vorgegebene Antragsgliederung bereits in Englisch formatiert. Die Ausgestaltung muss der unten aufgeführten Antragsgliederung ("**Guideline for Project Application**") entsprechen. Der Umfang soll **5 Seiten für das übergeordnete Verbundkonzept (A) und 5 Seiten pro geplantes Teilprojekt (C)** nicht überschreiten. Im Falle der Beantragung einer diagnostischen Studie, ist eine detaillierte **Darstellung der diagnostischen Studie** entsprechend den Vorgaben des Leitfadens (B) erforderlich. Diese soll **12 Seiten** nicht überschreiten (DIN-A-4 Format, 1,5-zeilig, Arial Schriftgröße 11).

Neben diesem Leitfaden gelten weiterhin die entsprechenden Merkblätter und Richtlinien des BMBF, soweit in diesem Leitfaden nicht ausdrücklich andere Regelungen getroffen sind. Weiterführende Links für die Antragstellung finden Sie auf den Internetseiten des BMBF³. Die dort veröffentlichten Anforderungen/Informationen werden regelmäßig aktualisiert. Eine Durchsicht vor dem Einreichen eines förmlichen Antrages (zweite Verfahrensstufe) wird dringend empfohlen.

Es wird dringend empfohlen zur Antragsberatung mit dem Projektträger Kontakt aufzunehmen. Weitere Informationen und Erläuterungen sind dort erhältlich. Ansprechpartner sind Dr. Isabella Napoli (Tel: 0228-3821-747) und Dr. Marina Schindel (0228-3821-776).

³ <http://www.foerderportal.bund.de/>

Guideline for Project Application

Applications that fail to comply with the requirements of this guideline will be considered as not eligible and will be rejected without further review.

A) DESCRIPTION OF CONSORTIUM

The overall description of the consortium should not exceed 5 pages

1. GENERAL INFORMATION ON THE CONSORTIUM

TITLE OF THE CONSORTIUM	The title of the project proposal of the consortium should be concise and brief (not exceeding 140 characters). Please also indicate an acronym derived from the title (max. 15 characters).
COORDINATOR	<ul style="list-style-type: none">• First name, last name, academic title of the coordinator• Institution and department (complete name)• Postal address• Telephone contact• Fax number• E-mail address
DISEASE AND DIAGNOSTIC PROBLEM	Please state the disease and the related diagnostic problem not exceeding 140 characters.
DURATION OF PROJECT	Please indicate the duration of the project (up to 36 months).
SUMMARY	Give a concise summary of the central idea and concept of the project (max. 1600 characters).

2. OBJECTIVES, INNOVATION AND RELEVANCE

2.1. DIAGNOSTIC PROBLEM

What is the diagnostic/medical problem? What is the diagnostic/medical need to be addressed (e.g. earlier/better diagnosis/prognosis, therapy monitoring)? What results are expected?

2.2. PROOF OF PRINCIPLE

Please provide detailed information on the evidence or preliminary results underlying this biomarker proposal (e.g. existing 'proof of principle', patents, publications).

2.3. SCIENTIFIC CONCEPT AND OBJECTIVES

Please describe the scientific background and the overall topic, concept, goals and methodological approaches of the entire project. Delineate the state-of-the-art in the field, line out your validation concept and refer to the established reference method ('gold-standard').

2.4. NOVEL ASPECT AND FUTURE IMPACT

What is the novel aspect of the proposed biomarker? Specify the impact and consequences of the results on clinical practice (e.g. prevention, diagnosis, prognosis of disease or therapy, and therapy control) and stress the innovative aspects of the project.

2.5. STRATEGIES FOR THE EXPLOITATION / DISSEMINATION OF RESULTS

Please indicate how the expected results of the project will be transferred into practise. Describe how the results of the research will either be disseminated to potential users or

how they will be commercialized. Please refer to strategies beyond publication in scientific journals. Indicate the role of the industrial partner, if applicable, for the exploitation of the results.

3. STRUCTURE OF THE PLANNED COOPERATION

3.1. PROJECT PARTNERS OF THE CONSORTIUM

Please characterize the participating project partners by filling in the table below. (A 'project partner' is a workgroup at a distinct institution, which accomplishes a well-defined work package or packages within the consortium).

No.	Principal investigator	Institution	Title of the sub-project	Function of the partner within the consortium
1	<i>e.g. Prof. Dr. Hans Muster</i>	<i>e.g. University..</i>	<i>e.g. Validation of...</i>	<i>e.g. Coordinator. Monitoring and evaluation of...</i>
2	<i>e.g. Dr. Ernst Hurtig</i>	<i>e.g. abc GmbH</i>	<i>e.g. Production of...</i>	<i>e.g. Processing of...</i>
3
...	...			
...				

3.2. COOPERATION, COORDINATION AND COMMUNICATION

Which structure will be implemented for an efficient cooperation within the consortium? How will the consortium be managed? Which are the contributions of the individual partners? Comment on the synergistic effects of interaction within the consortium and possible perspectives for the improvement of cooperation between industrial and academic research in biomarker validation.

3.3. ACCESS TO PATIENT COHORTS OR BIOMATERIAL BANK (BMB)

For the validation of biomarkers the access to patient cohorts or BMB, respectively the access to large, well-characterized collectives, is mandatory. Please refer in detail to this issue (for details see Part B, 2.3 Resources).

3.4. WORK PLAN AND MILESTONES

Please give an overview of the work plan of the network project (work-packages, milestones, time-frame).

4. FINANCIAL PLAN OF THE CONSORTIUM

No.	Partner	Total costs of project (€)	Applied BMBF funds (€)	Co-financed by industry or other sources (€)
1	<i>e.g. University...</i>	<i>500.000</i>	<i>500.000</i>	<i>0</i>
2	<i>e.g. abc GmbH</i>	<i>420.000</i>	<i>210.000</i>	<i>210.000</i>
3
...	...			
	Total	<i>920.000</i>	<i>710.000</i>	<i>210.000</i>

B) DIAGNOSTIC STUDY OUTLINE APPLICATION

A diagnostic study validates a biomarker in respect to the informational value. Diagnostic studies should be conceived on the basis of already existing clinical data and biomarker (retrospective trial) or on the basis of a prospective clinical trial. In both cases the following outline should be used, where applicable specific sub items can be skipped. In addition to the diagnostic study, there is the possibility to apply for funding of preclinical research projects which consider technical or methodological aspects of the study (Part C).

Please prepare your application in English not exceeding 12 pages (DIN A4, at least 11 point Arial). The number of pages includes cited literature. For the information of the reviewers, refer to the respective chapter in the trial protocol for further details if necessary. **Handwritten signatures of principal / coordinating investigator and responsible biostatistician are mandatory on the confirmation of the electronic submission of the application. Submit application, appendix, and the trial protocol according to GCP.**

1. STUDY SYNOPSIS

APPLICANT/COORDINATING INVESTIGATOR	Name, address, telephone, fax, e-mail In case of multiple applicants the principal investigator/coordinating investigator ⁴ of the trial who will assume responsibility for conducting the clinical trial, should be listed first.
TITLE OF STUDY	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.
OBJECTIVE(S)	Which principal research questions are to be addressed? Specify clearly the primary hypotheses of the trial that determines sample size calculation.
STUDY DESIGN	retrospective trial on existing clinical data and/or biomarker or a prospective clinical trial (i.e. randomized/non-randomized, type of masking)
VALIDATION CRITERIA	Specify clearly the main reference test (gold standard) for diagnostic marker or the clinical finding (prognostic marker)
KEY INCLUSION AND EXCLUSION CRITERIA	Key inclusion criteria: Key exclusion criteria:
OUTCOME(S)	Primary efficacy endpoint: Key secondary endpoint(s): Assessment of safety:
STATISTICAL ANALYSIS	Efficacy / test accuracy: Description of the primary efficacy / test accuracy analysis and population: Safety: Secondary endpoints:

⁴ "Investigator" as defined in the harmonised "Guideline for Good Clinical Practice" of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH GCP)(<http://www.emea.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."

SAMPLE SIZE	To be assessed for eligibility (n = ...) To be allocated to trial (n = ...) To be analysed (n = ...)
TRIAL DURATION	First patient in to last patient out (months): Duration of the entire trial (months): Recruitment period (months):
PARTICIPATING CENTERS	How many centres will be involved? (n)
SUMMARY	Give a concise summary of the project regarding the central idea, design, patients and expected results of the study (max. 1600 characters).

2. INNOVATION AND RELEVANCE

2.1. EVIDENCE

Set your study into perspective: Which studies have been conducted either by you or by others? Give references to any relevant systematic review(s)⁵ and/or (own) pilot studies, feasibility studies, relevant previous/ongoing trials, case reports/ series. If you believe that no relevant previous trials have been done, give details of your search strategy for existing information. This should both detail the background of the starting hypotheses and the feasibility of the trial.

2.2. THE NEED FOR A DIAGNOSTIC STUDY

How significant is the trial in terms of its potential impact in respect to better strategies for diagnosis, prognosis and therapy control and/or the knowledge of the underlying disease? What impact will the results have on clinical practice? Is the trial necessary at this point? Describe the added value of the test. How will a) the individual patient and b) the society/science benefit from the trial? Please describe the reproducibility, clinical consequences, definition for limits of the test, handling with intermediate or missing results, decision rules for multiple markers.

2.3. RESOURCES

Type

Is the study based on (already characterized) biomaterial bank (BMB), sample collection and/or patient cohorts? Describe in detail the type of collection (central/decentral) and how the access to the resources is organized in the consortium and participating institutions. Please characterize your available material collection according following issues:

- Which biological material is collected (nature [tissue or sample type] and numbers)?
- Comment on the primary goal of the material collection:
 - a) Is the material primarily stored for routine diagnostic or therapeutic purposes? Can the material additionally used for for research questions? If applicable, to which degree is this already undertaken? Is the treatment context embedded in a clinical study (purpose commitment)? If applicable, to which degree is this already undertaken?
 - b) Is the material only sampled and stored for research question(s)?
- Are you planning to receive or do you have already received the approval to use clinical/genetic/pathological data for your specific research question? Specify ethical issues regarding e.g. informed consent, declaration of appropriation, personal rights.

Population to be studied

⁵ For definition of a systematic review, see Oxman, AD (1994). Checklists for review articles, BMJ; 309; 648-51.

- Describe and justify, if applicable, the patient population to be studied (inclusion/exclusion criteria). Which standards are used for the classification of diagnosis and disease stages? How are patients for material collection selected and recruited?

Data and Material Acquisition and Storage

Describe the concept of data and material acquisition and storage.

- Which data are intended to be sampled and stored (data of patient, data of the sample(s), data of sample analysis)?
- Describe, if applicable, yet obtained numbers and comment on data protection.
- Does the database, or is intended to contain clinical, genetic or pathological information?
- Who does or will provide that input and where?
- Who is responsible for update and maintenance of the data base?
- Which instruments will be used to record the data? Are the instruments validated and reliable?
- How will the personal responsible for data acquisition be trained?
- Which standards will be used to classify diagnoses and stages of the disease(s)?
- Comment on the potential accessibility of related resources and on the possibilities to use or integrate already existing sources or data.

Ownership

Who will be/is the owner of the BMB? Who is owner of the collected samples in the BMB? Do you plan to delegate property rights or rights of use (without acquisition of property rights)? If yes, how can you assure that there is compliance with all different regulations?

Feasibility of comprehensive sampling

What is the evidence that the intended recruitment rate and total number of samples/patients for the BMB is achievable? In case of existing (systematic) collections, which publications of the last 2 years are based on this material bank?

International collaborations

If the proposed BMB includes non-German centres or collaboration with organisations in other countries please give full details of funding arrangements agreed or under consideration.

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 there a gold standard? What is the rationale for the units, cut off and/or categories?

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? Justify appropriateness and limitations of composite endpoints, if applicable.

Determination of primary and secondary measures

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

3.4. METHODS AGAINST BIAS

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

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. 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.

3.6. COMPLIANCE/RATE OF LOSS TO FOLLOW UP

Provide details for assumptions on compliance issues of the biomarker measure. 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?

3.7. 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.

3.8. 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 a) for the individual patient and b) for the whole trial if applicable.

4. STATISTICAL ANALYSES

What is the proposed strategy of statistical analysis?

Does the analysis include a search-and-validate strategy, i.e. by an explorative and confirmatory part? If so, please specify. What will be the primary data analysis set? 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, purpose commitment declaration, care and protection for research participants, protection of research participants' confidentiality, informed consent process, interest in property, personal rights).

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).

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 and list under 7.*

7. LIST OF PARTICIPANTS INVOLVED IN THE TRIAL

Trial Management *

#	Name	Affiliation	Responsibility/Role	Signature

Trial statistician			
#	Name	Affiliation	Signature
Participating centres/clinics (please provide signatures on declaration of commitment)			
#	Name	Affiliation (only institution and city, no complete address)	Expected no. of patients recruited for the complete trial
Total sum of recruited patients			$\Sigma =$
Trial Supporting facilities (i.e. central laboratories)			
#	Name	Affiliation	Responsibility/Role
Data Monitoring and Safety Board (DMSB)			
#	Name	Affiliation (only institution and city, no complete address)	

* It is mandatory for the trial management to have expertise in diagnostic/clinical studies. Please verify this by a list of publications and/or ongoing studies.

8. REFERENCES

Please list the most relevant publications (5-10) for this proposal.

9. TRIAL TIMELINE FLOW

As funding will critically depend on the study progression according to milestones, please provide a diagram reflecting milestones, recruitment status and data cleaning/analysis.

10. FINANCIAL DETAILS OF THE TRIAL

10.1. COMMERCIAL INTEREST

Please justify, why this diagnostic trial should be funded by a public funding agency and describe any potential commercial interest of a company (i.e. IP rights).

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 (€)". 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	TVÖD/ BAT	Total months	Total (€)	year 1 (months/€)	year 2 (months/€)	year 3 (months/€)
1	Clinical project management									
2	Project management									
3	Data Management									
4	Biometry									
5	Quality Assurance/ Monitoring		if applicable: number of visits per site mean number of days per visit monitoring costs per day total no of visits (€ / visit)							
6	Trial committees	no. of DSMB members	no. of meetings (€ / person)							
7	Meetings/ Travel	no. of attendees	no. of meetings (€ / person) 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 (€ / sample)							
10	Materials		consumables trial manuals, files, forms							
11	Fees									
12	Publications/Patents									
13	Equipment									
14	Other									
TOTAL							€	€	€	€

size of this table max. ONE page; submit copy as Excel file

months = staff indicated in months where applicable; €= other expenditures indicated in Euro where applicable

10.3. 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.

10.4. CO-FINANCING BY INDUSTRY AND/OR OTHER THIRD PARTIES

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

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

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

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

10.5. OTHER FUNDING

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

If this is not the case please declare:

"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."

11. STUDY PROTOCOL IN ACCORDANCE WITH ICH GCP

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

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

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

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

C) DESCRIPTION OF PRECLINICAL SUBPROJECTS FOR TECHNOLOGICAL OR SPECIFIC ASSAY DEVELOPMENT PURPOSES

In addition to diagnostic studies, preclinical research projects may be included which assess technical issues. The description of each preclinical research project should not exceed 5 pages maximum.

1. GENERAL INFORMATION ON THE PROJECT

TITLE	The title of the subproject (not exceeding 140 characters) should be precise. In case of funding this title shall be quoted in the annual reports of the funding organisation.
PRINCIPLE INVESTIGATOR OF THE SUBPROJECT	Name, address, telephone, fax, e-mail <ul style="list-style-type: none"> • First name, last name, academic title • Institution and department (complete name) • Postal address • Telephone • Fax • E-mail address
OBJECTIVE(S)	Which principal research questions are to be addressed? Specify clearly the primary goal of the subproject. Which results are expected? (not exceeding 140 characters)
DURATION OF PROJECT	In month. Please quote i) the time period for which funding is requested (max. 3 years) and ii), the date when funding should begin.
SUMMARY	Please give a summary of the main goals of the subproject (max. 1200 characters).

2. OBJECTIVES, INNOVATION AND RELEVANCE

2.1. HYPOTHESIS / RESEARCH GOAL

What is the hypothesis to be tested? What is the aim/purpose of the subproject? What results are expected?

2.2. NOVEL ASPECT AND FUTURE IMPACT

Briefly describe the state of the art and how the proposed subproject extends beyond it. What is the relevance of the subproject in the context of the consortium?

2.3. METHODS

Please describe briefly the methods you intend to apply.

2.4. SCIENTIFIC DISCIPLINE AND PREVIOUS WORK

Please name your discipline and your special field of work. Describe the major findings of your previous work. Give 5 of your most relevant publications of the past 3 years.

2.5. WORKING PLAN INCLUDING MILESTONES

Please describe the work packages, the milestones you plan to achieve and the necessary time frame.

2.6. COMPLIANCE WITH GLP

If an approval of the novel diagnostic tool/biomarker is intended, please indicate how the preclinical research will be conducted in compliance with the requirements of GLP (good laboratory practice) standards.

2.7. FINANCIAL PLAN

Please structure the financial plan by completing the table “financial plan for subproject No...” as outlined below.

2.8. CO-FINANCING

Please indicate any co-financing of the studies by industry or other sources.

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

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

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

- Describe the type and volume of support (including any services or consumables provided free of charge).
- 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 BMB 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 a formal notion of award has been received; please contact the funding organisation first! Appropriate agreements on intellectual property, confidentiality, publication of results, property rights must be concluded between all cooperation partners prior to the conduct of the project. Reference is made to the legal provisions relevant to cooperation between industry, medical institutions and their staff.⁶

2.9. OTHER FUNDING

In case you have already submitted parts of the same request to other institutions or the BMBF, please mention this here. Indicate other sources which will provide funds, free services or consumables. 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.

2.10. DISSEMINATION AND EXPLOITATION STRATEGIES

Please indicate how the expected results of the project will be used. Describe the proposed arrangements for disseminating the results of the research to potential users.

⁶ Detailed information can be found in particular in the “Gemeinsamer Standpunkt zur strafrechtlichen Bewertung der Zusammenarbeit zwischen Industrie, medizinischen Einrichtungen und deren Mitarbeitern” (Common position concerning the consideration of cooperation between industry, medical institutions and their staff from the aspect of criminal law) published by the Verband forschender Arzneimittelhersteller (Association of Research-Based Pharmaceutical Companies) (<http://www.vfa.de/de/vfa/gemeinsamerstandpunkt.html>)

Appendix: Financial Plan for Project No. ...

Type of expenditure	person months	Costs (EUR)	Total of BMBF funds applied (EUR)	Co-financed by industry or others (EUR)
PERSONNEL				
Scientist*				
Non scientist*				
Others*				
OVERHEAD				
CONSUMABLES	---			
EQUIPMENT (to specify)	---			
TRAVEL (to specify)	---			
SUBCONTRACTS	---			
OTHERS (to specify)	---			
TOTAL of BMBF funds applied				
TOTAL of co-financed by other sources				

* Please use global employment rates of the BMBF for calculating the salaries

(Insert lines according to space required)