Leitfaden für die Erstellung von Projektskizzen zur „Richtlinie zur Förderung von Translationsprojekten Personalisierte Medizin“ – Modul 1 –

Der vorliegende Leitfaden enthält Informationen für die Erstellung und Einreichung von beurteilungsfähigen Projektskizzen. Er ergänzt die am 27. März 2020 im Bundesanzeiger veröffentlichte o.g. Förderrichtlinie (http://www.gesundheitsforschung-bmbf.de/de/10048.php).

Es wird dringend empfohlen, zur Beratung mit dem DLR Projektträger Kontakt aufzunehmen. Ansprechpartnerinnen sind:

Frau Dr. Alexandra Becker
Frau Dr. Christine Hasenauer
Frau Dr. Ute Preuß

Telefon: 0228-3821 1210; E-Mail: indimed@dlr.de

Entscheidungsverfahren

Im Modul 1 „Entwicklung neuer Diagnostik und Therapien für die PM“ ist ein fachlicher Begutachtungsschritt vorgesehen. Die eingegangenen Projektskizzen werden von einem unabhängigen Begutachtungsgremium anhand der in den Förderrichtlinien genannten Kriterien bewertet. Auf der Grundlage der Bewertung des Gremiums werden die für eine Förderung geeigneten Projekte ausgewählt.
Antragstellende, deren Projektskizzen für eine Förderung ausgewählt werden, werden aufgefordert einen förmlichen Förderantrag einzureichen (siehe Nr.7.4 der Förderrichtlinien).
Anträge, die vom Begutachtungsgremium nicht zur Förderung empfohlen werden oder die nicht den Vorgaben entsprechen, werden nicht gefördert.

Was wird gefördert?

Diagnostik: Entwicklung und Validierung von Biomarkern
In Modul 1 werden Forschungsverbünde zur Weiterentwicklung und Validierung von Biomarkern zur Stratifizierung von Patientengruppen, Krankheitsverlauf und Therapieantwort sowie zur zielgerichteten Präventionsdiagnostik gefördert. Forschungsprojekte können unter anderem auf die Entwicklung und Validierung diagnostischer, prädiktiver oder prognostischer Biomarker ausgerichtet sein. Die Identifizierung neuer Biomarker sowie Biomarker ohne Stratifizierungspotential sind nicht Gegenstand der Fördermaßnahme, hingegen kann die Repositionierung bekannter Biomarker in einem neuen Indikationsgebiet gefördert werden. Hierbei sollte für das neue Indikationsgebiet ein merklicher Innovationsschritt erfolgen. Das Stratifizierungspotential des Biomarker-Kandidaten ist im Antrag durch Publikationen oder Schutzrechte zu belegen. In der Projektskizze muss die Bedeutung des Biomarkers für das entsprechende Indikationsgebiet sowie eine Strategie dargelegt werden, wie der Biomarker validiert werden soll.

Therapie: Präklinische Forschung zu neuartigen, indikationsbezogenen Therapien
Ebenso werden in Modul 1 Forschungsverbünde gefördert, die die Machbarkeit eines indikationsbezogenen therapeutischen Ansatzes für die PM durch explorative und/oder konfirmatorische Studien im Tiermodell nachweisen sowie weitergehende Untersuchungen im krankheitsrelevanten präklinischen Modell durchführen wollen.

Voraussetzung für eine Förderung sind Vorarbeiten, die das Potential eines Therapieansatzes für eine personalisierte Behandlung belegen. Dies muss durch entsprechende Publikationen oder Schutzrechtsanmeldungen belegt werden. Die (tier-)experimentellen Modelle müssen eine hohe Relevanz für die angestrebte Indikation besitzen.

Als neuartige Therapieansätze werden vor allem folgende Ansätze definiert:
a) biotechnologisch-bearbeitete Gewebeprodukte (z. B. regenerative Verfahren);
b) biologische Substanzen („Biologicals“);
c) somatische Zelltherapien (z. B. regenerative Therapien, Immuntherapien);
d) gentherapeutische Ansätze;
e) kleine Moleküle;
f) präventive und therapeutische Impfstoffe, ausgenommen sind allgemeine Impfstoffe für Infektionen.

In beiden Bereichen sollen modernste Methoden und vorhandene Kohorten, Biobanken und Datenquellen genutzt werden. Die Forschungsverbünde sollen sich mit gesundheitspolitisch und gesundheitsökonomisch wichtigen Krankheitsgebieten befassen, bei denen personalisierte Behandlungsansätze noch nicht so weit fortgeschritten sind. **Krebserkrankungen und seltene Erkrankungen sind von einer Förderung ausgeschlossen.**

Die Projekte können in der Regel für einen Zeitraum von bis zu **drei Jahren** gefördert werden.

In dieser Fördermaßnahme werden ausdrücklich **nicht gefördert**
- chirurgische Methoden und Strahlentherapie,
- psychologische Behandlungsverfahren
- Entwicklung von Tiermodellen,
- Identifizierung von Biomarkern,
- Entwicklung spezifischer Assays oder Testsysteme,
- *de novo* Aufbau von Forschungsressourcen und -infrastruktur

Vorgaben für die Zusammensetzung der Projektkonsortien

Dieses Modul richtet sich an klinische und experimentelle Arbeitsgruppen aus universitären und außeruniversitären Forschungseinrichtungen sowie industrielle Partner, die in Verbünden zusammenarbeiten. Eine Beteiligung von Partnern aus der Wirtschaft ist erwünscht, aber nicht obligatorisch.
Staatliche und nicht-staatliche Hochschulen sowie außeruniversitäre Forschungseinrichtungen können bis zu 100% ihrer projektbezogenen Ausgaben bzw. Kosten beantragen.

Hochschulen kann zudem die sogenannte „Projektpauschale“ (20% der Zuwendung) gewährt werden. Weitere Hinweise dazu finden Sie unter:
https://foerderportal.bund.de/easy/easy_index.php?auswahl=easy_formulare&formularschrank=bmbf&menue=block (Menüpunkt „Zuwendungen auf Ausgabenbasis“).
Die Projektpauschale ist in der Kalkulation der Finanzplanung zu berücksichtigen.

Für Unternehmen der gewerblichen Wirtschaft mit FuE-Kapazität in Deutschland gilt in der Regel eine Förderquote von bis zu 50% der projektbezogenen Kosten zuzüglich gegebenenfalls zu gewährender Boni für KMU.

Allgemeine Hinweise

Wissenschaftliche Standards

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

- Handreichung der Senatskommission für tierexperimentelle Forschung der DFG zur Planung und Beschreibung tierexperimenteller Forschungsprojekte[1]
- ARRIVE Guidelines[2]
- PREPARE Guidelines
- Leitlinie zur Guten Zellkulturpraxis (Good Cell Culture Practice, GCCP)

Verwertungs- und Nutzungsmöglichkeiten

Die Aussichten für eine klinische Anwendbarkeit sind in der Projektskizze darzustellen. Zudem sind die für eine weitere klinische Entwicklung bzw. Umsetzung in die Versorgungspraxis notwendigen nächsten Schritte zu konzipieren. Die Antragstellenden haben darzulegen, ob sie eigene Schutzrechte haben und ob Schutzrechte existieren, die der weiteren Entwicklung im Weg stehen. Darüber hinaus ist darzustellen, inwieweit die Erlangung weiterer Schutzrechte angestrebt wird. Die Antragstellenden sollen idealerweise bereits ein Unternehmen kontaktiert haben, das bei positiven Ergebnissen die weiteren Schritte der klinischen Entwicklung übernimmt. Falls kein kommerzielles Interesse an einer Weiterentwicklung besteht, müssen andere Wege zur Weiterentwicklung dargestellt werden. Alle für die Umsetzung der Ergebnisse in die Praxis relevanten Nutzer und Akteure müssen frühzeitig als Kooperationspartner in die Vorhaben eingebunden werden. Unter dem Transfer von Forschungsergebnissen in die Praxis werden hier alle Aktivitäten verstanden, die über die wissenschaftsimmanente Verwertung (z. B. Publikationen in Fachmedien, Vorträge auf Fachkongressen) hinausgehen und die konkrete Implementierung von Forschungsergebnissen in der Praxis umsetzen.

Bonität

Unternehmen der gewerblichen Wirtschaft können nur dann gefördert werden, wenn die Bonität des Unternehmens gesichert ist. Der Förderer behält sich daher vor, geeignete Unterlagen (z. B. testierte Jahresabschlüsse, Lageberichte, Betriebswirtschaftliche Auswertung) 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.

Einreichen von Projektskizzen

Die Projektskizzen sind elektronisch unter https://ptoutline.eu/app/translation_pm_m1 spätestens bis zum

30. Juni 2020 24.00 (MESZ)

einzureichen. Eine vollständige Projektskizze umfasst eine Projektübersicht (ausgefülltes und verbindlich eingereichtes PT-Outline Internet-Formular) und die Projektbeschreibung in englischer Sprache (in einem PDF-Dokument zusammengefasste ausgefüllte Mustervorlagen).

Der Skizze ist ein Anschreiben/Vorblatt zur Einreichung beizulegen, auf dem Vertreter aller Projektpartner (in der Regeln die Projektleiterinnen bzw. Projektleiter) mittels rechtsverbindlicher Unterschrift die Kenntnisnahme sowie die Richtigkeit der in der Skizze gemachten Angaben bestätigen.

[1] https://www.dfg.de/download/pdf/dfg_im_profil/gremien/senat/tierexperimentelle_forschung/handreichung_sk_tierversuche.pdf
[2] https://www.biorxiv.org/content/biorxiv/early/2019/07/15/703181.full.pdf

Vorgaben für die Projektskizzen

Die Projektskizzen müssen den Vorgaben und der Formatierung der Mustervorlagen (Schriftart Arial, Schriftgrad 11, Zeilenabstand 1,5 Zeilen) entsprechen und **in englischer Sprache** verfasst werden. Die vorgegebenen Seitenzahlen dürfen nicht überschritten werden. Die Kopfzeile soll das Akronym des Konsortiums sowie die Benennung des Antragsteils (Beschreibung des Konsortiums /Beschreibung des präklinischen Teilprojektes etc.) enthalten. Anträge, die diese formalen Vorgaben nicht erfüllen, können von der Bewertung ausgeschlossen und ohne weitere Begründung abgelehnt werden.

Der Koordinator bzw. die Koordinatorin erstellt aus den notwendigen Mustervorlagen **ein einzelnes PDF Dokument** für das Projekt. Welche Mustervorlagen für Ihren Antrag erforderlich sind, entnehmen Sie bitte der folgenden Liste:

1.) **"Description of Consortium"** (max. 6 Seiten inklusive 1 Seite Beschreibung der Verwertung)
http://www.dlr.de/pt/Portaldata/45/Resources/Dokumente/GF/Mustervorlage_Description_of_Consortium_Modul1.docx
2.) **"Preclinical Subproject"** (max. 5 Seiten) und/oder
http://www.dlr.de/pt/Portaldata/45/Resources/Dokumente/GF/Mustervorlage_Preclinical_Subproject_Modul1.docx
3.) **"Diagnostic Study"** (max. 5 Seiten) und/oder
http://www.dlr.de/pt/Portaldata/45/Resources/Dokumente/GF/Mustervorlage_Diagnostic_Study_Modul1.docx
4.) **"Preclinical Confirmatory Study"** (max. 5 Seiten)
http://www.dlr.de/pt/Portaldata/45/Resources/Dokumente/GF/Mustervorlage_Preclinical_Confirmatory_Study_Modul1.docx

Mustervorlagen für die Projektskizzen

Nachfolgend finden Sie die Mustervorlagen mit Erläuterungen für die Projektskizzen. Die entsprechenden word.docx Dateien mit den Überschriften finden Sie unter den oben angeführten Internet-Links.

1. Template: Description of Consortium

This part of the application should not exceed 6 pages <u>including max. 1 page</u> description of the exploitation (DIN A4, minimum of 11 point Arial, line spacing 1.5 lines). *It has to be understandable without reading the cited literature and without consulting further literature. Attachments are not permitted (neither CVs, patent applications, publications nor study protocols). Here, the general information on the project at consortium level should be provided including an overview of all subprojects, while the detailed description of the preclinical work in the respective subprojects should be based on the corresponding template. Duplications are to be avoided as far as possible.*

1. Title of Consortium

The title of the consortium (max. 140 characters) should be as precise as possible. In case of funding, this title will be quoted in the annual reports of the funding organisation. Please indicate an acronym (max. 40 characters) derived from the title of the project and change the header, accordingly.

2. Project Coordinator

Academic title, first name, last name, institution

3. Research Question(s)

3.1 Aims and Objectives

What is the project aiming to achieve? Give a concise description of your project's objectives; list them in order of priority. State your working hypotheses/rationale. Which disease entity(ies) should be addressed in the consortium?

3.2 Novelty and Future Impact

What is the novelty of the proposed research question? Describe the innovative approach and development stage of diagnostic/ therapeutic concept. Specify the impact of the expected results on personalized medicine and clinical practice: therapeutic benefit, including improvement of health and life quality of patient groups targeted.

3.3 Scientific Background and Preliminary Data

Give sufficient details of past and current research to show that the aims are scientifically justified and to show that the work will add distinct value to what is already known, or in progress. Shortly discuss competing approaches and how far advanced these are in comparison to the planned project aims, if applicable.

3.4 Description of Consortium Organization

What structure is available respectively will be implemented for an efficient cooperation within the consortium. How will the consortium be managed? Define subprojects; in case of multiple investigators, if applicable. Indicate which tasks will be taken over by whom in the different subprojects.

Example:

Subproject No.	Partner	Title of Subproject	Function in the consortium
1	*University of…*	*Preclinical evaluation of novel XY for the treatment of heart failure*	*Coordination; performing preclinical research, processing of results*
	abc GmbH	*Statistical analysis*	*Subcontractor of University of … for ……*
2	*University of…*	*Analysis of blood samples*	*Clinical partner for validation of biomarker*

Please note: Subcontractors have to be indicated in case of contract volume above 100.000 €.

3.5 Work Programme

Give an overview on the general experimental approaches. It is not necessary to describe each experiment, but enough detail must be given to show why the research is likely to be competitive in its field. In case of multiple investigators: indicate which tasks will be taken over by whom in the different subprojects.

3.6 Milestone Plan

Indicate work packages into which the project is divided and schedule events that indicate the completion of major deliverable events. Milestones are measurable/observable events and serve as progress markers.

Example:

WP no.	*Milestone (▼)*	*year 1*	*year 2*	*year 3*
1	*Animal experiments approval granted*	▼		
2	*Experimental setup and system modification completed*	▼		
3	*Data acquisition and analysis*			▼

4. Data Handling

If research data or information is to be systematically produced, describe if and how these will be made available in your consortium and for future reuse.

5. Gender Aspects

Describe how you consider gender aspects as a significant variable in your research plan. If not, please explain why gender aspects are not relevant for your research question.

6. Ethical and Legal Consideration

Please give a description of ethical considerations relating to the project (assessment of risks and benefits, purpose commitment declaration, interest in property, personal right).

7. Exploitation

Funding is provided in order to accelerate the development of new diagnostic and/or therapeutic processes and products which are of high medical relevance and economically viable.

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7.1 Intellectual Property Rights

Please explain Freedom to operate in respect to patent and exploitation strategy.

7.2 Expertise for Exploitation

Describe skills and expertise of the members of the consortium to promote the diagnostic/therapeutic/ theranostic approach and to drive into medical practice/therapeutic market.

7.3 Strategy for Exploitation

Describe the key steps of your strategy for the introduction into medical practice/therapeutic/diagnostic market.

8. Other Funding

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

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 of this project has not been submitted to any other addressee. In case I submit such a request I will inform the DLR Projektträger immediately.

9. References

Specify the most relevant publications of the past years (max. 10) and indicate the public access links if possible. ***Mark your own publications in bold****. For the references please use the Vancouver style (Further information: International Committee of Medical Journal Editors. Uniform Requirements for Manuscripts submitted to Biomedical Journals. NEJM 1997; 336:309-15). Additionally, in case of patent applications relevant to the project aims please indicate patent number/issue date or application serial number/application date, ideally with a link to the respective data base.* ***Only for the references and the patent applications a minimum of font Arial, font size 9, line spacing 1.0 lines is allowed.***

2. Template: Preclinical Subproject

Please number the respective subprojects according to the list given under “Template 1: Description of Consortium“, No. 3.4” “Description of consortium organization“. ***The description of each subproject should not exceed 5 pages (DIN A4, minimum of 11 point Arial, line spacing 1.5 lines).*** *Structure your application using the headings listed below and make an entry under every heading/subheading. Please continue with further subprojects numbered consecutively.*
The application has to be understandable without reading the cited literature and without consulting further literature. Attachments are not permitted (neither CVs, patent applications nor publications).

In case you want to apply for funding of a diagnostic study or a confirmatory study please use the additional templates No. 3 and/or No. 4.

1. Title of Subproject
Title of subproject (max. 140 characters).

2. Principal Investigator(s)
Academic title, first name, last name, institution of all PIs.

3. Subproject Description

3.1 Aim of the Subproject and Research Question(s)
Please describe the aims of the subproject and the research question(s) addressed. What results are expected?

3.2 Own Previous Work, Resources and Expertise
Which own previous work is directly relevant for the hypothesis and the research question(s)? Describe the necessary resources in place for the accomplishment of the project: infrastructure, capacities, specific expertises and previous achievements (e.g. methodologies, cells/tissues, animal models, patient cohorts etc.).

3.3 Research Approach
Describe the methodologies and technical approaches used in the subproject. How are the required resources integrated in the project?

3.4 Work Plan
Please describe your work plan in detail (work packages, time frame, milestones). Which tasks will be done? How will the aims of the subproject be reached? Please indicate how the preclinical research will be conducted in compliance with the requirements of GLP standards where required.

3.5 Added Value for the Consortium
Describe the cooperation with other consortium partners. What is the added value of this cooperation? What is the relevance of the subproject in the context of the consortium and the overall research question?

3.6 Milestone Plan
Indicate work packages into which the project is divided and schedule events that indicate the completion of major deliverable events. Milestones are measurable/observable events and serve as markers.

Example:

WP no.	*Milestone (▼)*	*year 1*	*year 2*	*year 3*
1	*Animal experiments approval granted*	▼		
2	*Experimental setup and system modification completed*		▼	
3	*Data acquisition and analysis*			▼

4. References

Please list the most relevant publications (max. 10) and indicate the public access links if possible. ***Mark your own publications in bold****. For the references please use the Vancouver style (Further information: International Committee of Medical Journal Editors. Uniform Requirements for Manuscripts submitted to Biomedical Journals. NEJM 1997; 336:309-15). Additionally, in case of patent applications relevant to the project aims please indicate patent number/issue date or application serial number/application date, ideally with a link to the respective data base.* ***Only for the references and the patent applications a minimum of font Arial, font size 9, line spacing 1.0 lines is allowed.***

3. Template: Diagnostic Study

The description of the diagnostic study should not exceed 5 pages (DIN A4, minimum of 11 point Arial, line spacing 1.5 lines). *The number of pages includes cited literature. Attachments are not permitted (neither CVs, patent applications nor publications). Structure your application using the headings listed below and make an entry under every heading/subheading.*
For planning a diagnostic study the checklist of the "STARD Statement" should be considered (Standards for the Reporting of Diagnostics Accuracy studies (http://www.equator-network.org/reporting-guidelines/stard/).
Most applications fail due to lack of information or information that is not very meaningful. In the case of the validation of a biomarker, applications often fail due to an inadequate or missing biostatistical validation concept.

Please note: *The signature of a biometrician at the end of the study synopsis is mandatory!*

1. Title of Subproject

Title of subproject (max. 140 characters).

2. Study Synopsis

PRINCIPAL INVESTIGATOR(S)	*Name, address, telephone, fax, e-mail* *In case of multiple applicants, the principal investigator[3] of the study who will assume responsibility for conducting the study should be listed first.*
TITLE OF STUDY	*The title of the study (not exceeding 140 characters) should be as precise as possible. In case of funding this title shall be quoted in the annual reports of the BMBF. Acronym is optional.*
MEDICAL CONDITION	*The medical condition being studied (e.g. asthma, myocardial infarction, depression).*
OBJECTIVE(S)	*Which principal research questions are to be addressed? Specify clearly the primary hypotheses of the study that determines sample size calculation. Specify precisely what the biomarker will be used for in clinical practice (diagnosis/prognosis/prediction).*
STUDY DESIGN	*e.g. retrospective study on existing clinical data and/or biomaterial bank*
VALIDATION CRITERIA	*Specify clearly the index test and the reference procedure (gold-standard) for diagnostic marker and/or clinical finding.*
KEY INCLUSION AND EXCLUSION CRITERIA	*Key inclusion criteria:* *Key exclusion criteria:*
OUTCOME MEASURE(S)	*Primary efficacy endpoint:* *Key secondary endpoint(s):* *Assessment of safety:*

[3] "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). This definition should be used accordingly for non-drug studies/studies: (1.34 Investigator) "A person responsible for the conduct of a clinical study at a study site. If a study is conducted by a team of individuals at a study 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 study."

STATISTICAL ANALYSIS	*Efficacy / test accuracy:* *Description of the primary efficacy / test accuracy analysis and population:* *Safety:* *Secondary endpoints:*
SAMPLE SIZE	*To be assessed for eligibility (n = …)* *To be allocated to study (n = …)* *To be analysed (n = …)*
STUDY DURATION	*Duration of the entire study (months)*
PARTICIPATING CENTERS	*To be involved (n): How many centres will be involved?*
SIGNATURE BIOMETRICIAN	

3. Scheme/Study flow

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

4. Medical Problem

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

4.1 Evidence

Set the study into perspective; substantiate the starting hypothesis. What is the rationale for the study? Give references to any relevant systematic review(s) and/or (own) pilot studies, feasibility studies, relevant previous/ongoing studies, case reports/series to support the candidate surrogate marker.

4.2 The Need for a Diagnostic Study

How significant is the study 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 and personaalized medicine? Is the study necessary at this point? How will a) the individual patient and b) the society/science benefit from the study? Please describe the reproducibility, clinical consequences, and definition for limits of the test, handling with intermediate or missing results, and decision rules for multiple markers.

4.3 Assay Performance Criteria

Please provide information on the performance criteria of the assay used in this study: reproducibility, feasibility (readily accessible, international standards available, calculated costs reasonable), confounders (assay related, non-assay related), and stability.

4.4 Resources

4.4.1 Type

Is the study based on an (already characterized) biomaterial bank (BMB), a 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 the available material collection and/or patient cohorts according to the following issues:
Which biological material is collected (nature [tissue or sample type] and numbers)?

Comment on the primary goal of the material collection and/or patient cohort:

a) Is the material primarily stored for routine diagnostic or therapeutic purposes? Can the material additionally be used for research questions? If applicable, to which degree is this already undertaken? Is the treatment context embedded in a clinical study (purpose commitment)?

b) Is the material only sampled and stored for research question(s)?

Is it planned to receive or is the use of clinical/genetic/pathological data for the specific research question already approved? Specify ethical issues regarding e.g. informed consent, declaration of appropriation, personal rights.

4.4.2 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 yet obtained numbers and comment on data protection. Does the database, contain (or 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 personnel 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.

4.4.3 Ownership

Who is the owner of the BMB and/or patient data from a cohort? Who is owner of the collected samples in the BMB? Will property rights or rights of use (without acquisition of property rights) be delegated? If yes, how is assured that there is compliance with all different regulations?

4.4.4 Feasibility of comprehensive sampling

In case of existing (systematic) collections and/or patient cohorts, which publications of the last 2 years are based on this material bank or patient cohort?

5. Justification of Design Parameters

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

5.1 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?

5.2 Inclusion/Exclusion Criteria

Justify the population to be studied (inclusion/exclusion criteria), include reflections on relevance for patient stratification and/ or personalisation of medical treatment, specifically with regard to gender and age. Which standards are used for the classification of diagnosis and disease stages?

5.3 Outcome Measures

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

5.4 Proposed Sample Size/Power Calculation

What is the proposed sample size and what is the justification for the assumptions underlying the power calculations? If the sample size is not based on statistical hypotheses justify why another approach has been chosen and why that enables to answer the medical question of the study.

5.5 International Collaborations

If the proposed study (incl. possible BMB) comprises foreign centres or collaboration with organisations in other countries please give full details of funding arrangements agreed or under consideration in the appendix.

6. Statistical Analyses

What is the proposed strategy of statistical analysis? What is the strategy for analysing the primary outcome? If interim analyses are planned, please specify. Are there any subgroup analyses? Discuss the robustness of the results e. g. with respect to unavoidable incomplete or missing data. If high-throughput data are generated (e.g. when using micro-arrays) which methods are used to adjust for multiplicity and an inflated error of false positive results?

7. Ethical Considerations

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

8. Quality Assurance and Safety

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 study site).

9. List of Participants involved in the Study

Please give details on roles/responsibility of involved personnel (study sponsor, study management, study statistician, study supporting facilities, recruiting centres, advisory board/study steering committee/DMSB if applicable).
*A final version of the study protocol has to be submitted to the funding agency together with the statement by the ethics committee **after** the review process. Funding of the actual study can only be provided if all necessary formal and legal requirements are met.*

10. Conflict of Interest

Any potential conflicts of interest must be disclosed.
The rules set forth in the “Guidelines for avoiding conflicts of interest” by the German Research Foundation (https://www.dfg.de/formulare/10_201/10_201_en.pdf) for advisory boards/study steering committees/DMSB have to be observed. In case of (co-)financing by industry or other third parties assure that the coordinating investigator is independent, in particular with regard to the analysis of the study and the publication of its results. For guidance please refer to the statement of the International Committee of Medical Journal Editors (ICMJE) http://download.thelancet.com/flatcontentassets/authors/icmje-statement.pdf.

11. References

*Please list the most relevant publications (max. 10 including references from point 4.1. Evidence) and indicate the public access links if possible. **Mark your own publications in bold**. For your references please use the Vancouver style (Further information: International Committee of Medical Journal Editors. Uniform Requirements for Manuscripts submitted to Biomedical Journals. NEJM 1997; 336:309-15). Additionally, in case of patent applications relevant to the project aims please indicate patent number/issue date or application serial number/application date, ideally with a link to the respective data base. **Only for the references and the patent applications a minimum of font Arial, font size 9, line spacing 1.0 lines is allowed.***

4. Template: Preclinical Confirmatory Study

The description of the preclinical confirmatory study should not exceed 5 pages (DIN A4, minimum of 11 point Arial, line spacing 1.5 lines). *The number of pages includes cited literature. Attachments are not permitted (neither CVs, patent applications nor publications). Structure your application using the headings listed below. Make an entry under each heading/subheading.*

Please note: *The signature of a biometrician at the end of the study synopsis is mandatory!*

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1. Title of the subproject

Title of the subproject (max. 140 characters).

2. Study Synopsis[4]

PRINCIPAL INVESTIGATOR(S)	*Name, address, telephone, fax, e-mail* *In case of multiple applicants the principal investigator / coordinating investigator of the study who will assume responsibility for conducting the study should be listed first.*
TITLE OF STUDY	*The title of the study (not exceeding 140 characters) should be as precise as possible. In case of funding this title shall be quoted in the annual reports of the BMBF. Acronym is optional.*
MEDICAL CONDITION	*Please describe the medical condition addressed*
OBJECTIVE(S)	*Which hypotheses are to be tested? Clearly specify the primary objective of the study that determines sample size calculation. Specify any secondary objectives.*
ETHICAL STATEMENT	*Discuss the acceptability of the harm incurred by the animals versus the potential benefit for the patients*
PARTICIPANTS/SETTING	*Provide details of the samples (animals, probes/samples of humans, cell cultures etc.) to be used e.g. species, strain, source, sex, age (developmental stage), genetic modification, weight; cell line, authentication and characterization, age and sex of donor, nature of tissue specimen,*
HOUSING AND HUSBANDRY	*Provide details of* • *housing (e.g. type of facility, type of cage) and husbandry conditions (e.g. food, water, light/dark cycle)* • *storage and banking*
INTERVENTION	*Provide details of the intervention(s) for each experimental group including controls; provide details of all experimental procedures to be carried out (How, when, Where, Why)* *Intervention:* *Control intervention (pos./neg.):* *Duration of intervention:* *Follow-up:*
STUDY DESIGN	*Please provide:* • *Number of experimental and control groups* • *Key inclusion and exclusion criteria* • *Consideration of external validity: age, sex of animals or samples, comorbidities, lab variety* • *Outcome: define the primary efficacy endpoint; key secondary endpoint(s)* • *Methods to reduce risk of bias: randomization and blinding, in/exclusion criteria, etc.*
SAMPLE SIZE	• *Specify the experimental unit of analysis for each dataset*

[4] *In preparation of the application the following information related to study design is worth noting:*
https://www.nc3rs.org.uk/experimental-design
https://www.nc3rs.org.uk/experimental-design-assistant-eda
https://www.nc3rs.org.uk/arrive-guidelines,
http://journals.sagepub.com/doi/10.1177/0023677217724823

CALCULATION, STATISTICAL ANALYSIS	• *Provide details of sample size calculation used (including rationale for the chosen effect size and statistical power). Motivate this by effect sizes from previous studies.* • *Specify the total number of animals / cell culture / samples to be used in each experiment, and the number of animals / cell culture / samples in each experimental group* • *Outline the statistical methods to be used for each analysis*
QUALITY CONTROL	1. *Provide information on the precautions to secure validity of test procedures (also across labs), authentication of biological resources (animals, cells, antibodies, media etc.), skills needed, standardized protocols, data management, (pre)registration, reporting guidelines*
TIME SCALE	*Time for preparation of the study (months):* *Time for the study:* *Time for data clearance and analysis (months):* *Duration of the entire study (months):*
PARTICIPATING LABS	*To be involved (n):* *How many labs will be involved? Please also list the cities.*
SIGNATURE BIOMETRICIAN	

3. Intervention Scheme / Study Flow

Provide a schematic diagram of the intervention.

4. Relevance / Impact of the Study

Which medical condition is to be addressed? Which principal research questions are to be addressed? How will your study affect the translational process? *Please describe the relevance of your approach in the context of answering the clinical question. What is the novel aspect of the proposed study?*

5. Scientific Premise / Previous Results

This section should detail the background of the starting hypotheses of the study.

Please provide the scientific premises to understand the motivation and context for the study:
Please describe previous results, e.g. explorative studies, triangulation, others. If they are published please provide the references. Which is the central finding that is to be confirmed? Also give evidence why a confirmatory study is justifiable at this stage.

6. Relevance of the Model

Which model is to be used? Please provide details for animal species / cell model, cell source / samples, age, sex. Please provide sound scientific reasoning why the chosen model can address the scientific objectives and the study´s relevance to human biology.

In case animal studies are planned please explain:
1. *why there are no realistic non-animal alternatives*
2. *how and why the animal species being used can address the scientific objectives and the relevance to human biology.*
3. *Is the (animal) model different from the previous / to be confirmed studies? If yes, why?*

7. Justification of Design Aspects

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

7.1 Control(s) / Comparator(s)

Justify the choice of control(s) / comparison(s). Which studies establish efficacy of the chosen positive control regimen?

7.2 Inclusion / Exclusion criteria

Justify the population to be studied, include reflections on generalisability and representativeness (external validity).

7.3 Intervention(s)

Justify the choice of your planned intervention(s) / treatment(s). Illustrate your intervention scheme graphically.

7.4 Outcome Measures

Justify the endpoints chosen (primary, secondary): Are the chosen endpoints relevant? Are there other studies that have utilized these endpoints?

7.5 Methods to reduce Risk of Bias

Describe possible risk of bias in your methods, conduct and analysis of your proposed study. Address risk of reporting bias, too. Describe e.g. procedures for randomization and blind in- and exclusion criteria, use of reporting guidelines, reporting of all results. If randomization or blinding is not possible please explain why and give details of alternative methods to avoid biased assessment of results.

7.6 Proposed Sample size / Power Calculations

What is the proposed sample size? This should be deduced from the previous study that is to be confirmed. What is the minimum clinically relevant effect size based on the previous results that is planned to be achieved with this confirmatory study? The minimum power for the confirmatory study should be > 90%. Also, clearly outline independence / dependence of experimental units (and nesting, if applicable). 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, as appropriate. It is important that the sample size calculations take into account anticipated rates of losses.

7.7 Feasibility

What is the evidence that the intended sample size is achievable? Comment on the access to animals / samples in labs of partner institutions and their willingness to cooperate in the study.

8. Statistical Analysis

What is the 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? How does the analysis parallel / deviate analysis strategies from the studies that are to be confirmed?

9. Quality Control

Comment on the precautions planned to secure validity of test procedures (also across labs), authentication of biological resources (animals, cells, antibodies, media etc.), skills needed, standardized protocols, (pre-) registration, data management, maintenance and long-term accessibility for future reuse of your results (also by third parties, taking into account privacy rules and proprietary data). (To ensure that your research data are soundly managed please follow the principle of FAIR data[5]. Please use existing standards and data repositories). Also mention at which stage data sharing will be ensured.

10. Ethical Considerations

If applicable:
Discuss briefly the acceptability of the harm incurred by the animals versus the potential benefit for the patients.

11. Study Management

11.1 Major Participants

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

#	Name	Affiliation	Responsibility/Role
			Principal/Coordinating Investigator
			Data management /Study Analysis
			Statistician
			……

11.2 Study Expertise

Please indicate study expertise of all above-mentioned participants by citing relevant publications and / or specifying major role in ongoing study(s) (to be identified; max. 5 publications of the last 3 years per person).

[5] http://www.forschungsdaten.org/index.php/FAIR_data_principles

Only for the references a minimum of font Arial, font size 9, line spacing 1.0 lines is allowed. *Ensure that the team of investigators has the necessary expertise to carry out the study.*

12. References

Please list the most relevant publications (max. 10 including references from point 5. Scientific Premise/ Previous Results) and indicate the public access links if possible. ***Mark your own publications in bold****. For your references please use the Vancouver style (Further information: International Committee of Medical Journal Editors. Uniform Requirements for Manuscripts submitted to Biomedical Journals. NEJM 1997; 336:309-15). Additionally, in case of patent applications relevant to the project aims please indicate patent number/issue date or application serial number/application date, ideally with a link to the respective data base.* ***Only for the references and the patent applications a minimum of font Arial, font size 9, line spacing 1.0 lines is allowed.***