**Mustervorlage & Erläuterungen für ausführliche Skizzen für präklinische konfirmatorische Studien**

**Full Proposal – Preclinical Confirmatory Study**

*To ensure comparability please prepare your proposal in English* ***not exceeding 28 pages for the headings 1.-12*** *(excluding the financial table) with the following format:**DIN A4, 11-point Arial, margins of at least 2 cm and single-spaced lines. Tables and references: 10-point Arial.*

*Please note: Pages exceeding the given limit will be removed before the evaluation.*

*Structure your application using the headings listed below.* ***Make an entry under each heading/subheading and address all listed points.*** *Text in italic in this template explains the expected information to be given by the applicants and should be replaced.*

*Additionally,* ***four appendices*** *are to be submitted: 1. Graphic study overview, 2. Data management plan, 3. Declaration by partners involved in the study, 4. CVs of major participants.*

*Do* ***not*** *submit any other appendices!*

***Signatures of the coordinator, PIs of participating laboratories and the study statistician are mandatory*** *in appendix 3 “Declaration of partners involved in the study”.*

# STUDY SYNOPSIS[[1]](#footnote-1)

|  |  |
| --- | --- |
| COORDINATING INVESTIGATOR | *Name, institution and department* |
| Participating LabORATORIES | *To be involved (n):**Name, institution and department* |
| TITLE OF STUDY | *Same title as in outline application* |
| Acronym | *Same acronym as in outline application* |
| MEDICAL FIELD  | *Please name the medical field(s) the study addresses* |
| Medical condition | *Please describe the medical condition addressed* |
| OBJECTIVE(S) | Objectives:*Which principal research question(s) are to be addressed? Clearly specify the primary objective of the study determining the sample size calculation. Specify any secondary objectives.*Hypothesis:*Define the hypothesis to be tested.*  |
| Model/setting | *Describe the models / samples (animals, probes/samples of humans, cell cultures etc.) to be used* |
| INTERVENTION | *Brief description of the experimental and the control treatments or interventions as well as dose and mode of application.** *Experimental Intervention*
* *Control intervention (pos. / neg.):*
* *Duration of intervention:*
* *Follow-up:*
 |
| STUDY DESIGN | *Please provide:** *Laboratories (labs) participating in the multicenter study*
* *Experimental and control groups*
* *Key inclusion and exclusion criteria*
* *Outcome: define the primary efficacy endpoint; key secondary endpoint(s)*
* *Methods to reduce risk of bias*
* *Parallel groups / crossover design*
 |
| Statistical Analysis | * *Brief outline of the statistical analyses including handling of missing data or clustering/hierarchical structures within the data*
* *Assumed effect sizes*
* *Description of the primary efficacy analysis and population*
 |
| SAMPLE SIZE CALCULATION | * *Experimental unit*
* *Sample size calculation used*
* *Number of animals / cell culture / samples to be used in each experiment, experimental group*
* *Total number of animals / cell culture / samples to be analyzed in each lab and in all labs together*
* *Statistical methods to be used*
 |
| Study Duration | * *Time for preparation of the study (months):*
* *Time for the study (months):*
* *Time for data clearance and analysis (months):*
* *Duration of the entire study (months):*
 |

# RESPONSE TO REVIEWERS’ COMMENTS

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

# SUMMARY

*Give a summary of the main aspects of the project (max. 1600 characters incl. blanks).*

# MEDICAL PROBLEM, RELEVANCE AND IMPACT

* *Which medical condition is to be addressed? Which therapy options are available for treatment of the disease? Which principal research questions are to be addressed?*
* *What is the novel aspect of the proposed study?*
* *Please describe the clinical relevance and impact of the study.*

# SCIENTIFIC PREMISE / PREVIOUS RESULTS

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

## Scientific premise

*Please provide the scientific premises to understand the motivation and context for the study.*

## Previous (own) results directly related to the planned study

* *Please describe previous results, e.g. explorative studies, triangulation, others. If they are published please provide the references. If not, please provide information at a level of detail that allows reviewers to assess the strength of evidence. That means methods (study design), analysis and results should be described, data should be presented in tables or figures and key figures (sample size per group, effect size, variance should be given).*
* *Which is the central finding that is to be confirmed?*
* *Explain why a confirmatory study is justifiable at this stage.*
* *Describe and justify deviations between the previous study and the proposed confirmatory study (e. g. additional strains, controls, differences in the analysis strategy, etc.).*

*Please note:*

*The experimental design of the confirmatory study should reflect the initial design of the exploratory study. Crucial factors like primary outcome, essential methods, and model should stay constant between exploratory and confirmatory phase. Deviations need to be spelled out, motivated, and strengthen validity. To strengthen validity, limited extensions are possible. That is, a confirmation is not necessarily a direct replication of the initial experiment. It is rather a test of the underlying knowledge claim and should enable decisions for future steps and translation into clinical contexts. For deviations regarding the number of experimental units see statistical analysis and planning in the* [*guidance document*](https://www.bihealth.org/fileadmin/QUEST/Publikationen/Bericht/DECIDE_Guidance_for_planning_and_conducting_confirmatory_preclinical_studies_and_systematic_reviews.pdf) *of the DECIDE project.*

# MODEL SYSTEM

## Relevance of the model

* *Which model/models is/are to be used: Please provide details for animal species / cell model, strain, sex, age (developmental stage), weight. Provide source of animals or cells, international nomenclature, genetic modification status, genotype, health/immune status, drug or test naive; cell line, authentication and characterization, age and sex of donor, nature of tissue specimen, storage and banking.*
* *Please provide sound scientific reasoning how and why the chosen model can address the scientific objectives and explain its relevance to the human disease.*
* *Reflect on generalisability and representativeness (external validity/ systematic heterogenization: age, sex, comorbidities, lab variety). How will intra- and inter-laboratory variation be considered?*

## Ethical considerations

* *In case animal studies are planned please also explain: Why are there no suitable non-animal alternatives?*
* *Discuss the acceptability of the harm incurred by the animals versus the potential benefit for the patients.*

# JUSTIFICATION OF DESIGN ASPECTS

*In the following: Please substantiate and do not only list the respective information.*

## Overview of planned study

* *Please describe the general set-up of the multicentre study (e. g. structure, subsequent steps (if applicable), number of experimental groups). Please also explain how many and which laboratories will be involved as well as which parts of the study will be carried out across these laboratories. Details can be given below.*
* *If applicable, describe additional planned experiments in individual laboratories (not exceeding 20% of the scope of the multicentre study) and explain their relevance for the study.*
* *Graphic study overview: Please illustrate the study graphically with a flow chart in appendix 1.*

## Control(s) / comparator(s)

*Give details and justify the choice of control(s) / comparison(s). Which studies establish efficacy of the chosen positive control regimen?*

## Inclusion / exclusion criteria

*Describe and justify the inclusion and exclusion criteria, the population to be studied.*

## Outcome measures

*Define and justify the endpoints chosen (primary, secondary). Why are the chosen endpoints relevant? Are there other studies that have utilized these endpoints?*

## Methods to reduce risk of bias

*Describe your strategy to handle possible risk of bias in your methods, conduct and analysis of your proposed study, also considering to ensure independence of study analysis from your previous study which is to be confirmed. Address the risk of reporting bias, too.*

*Please describe explicitly e.g.*

* *Procedures for randomization and blinding: Please detail your description how blinding and randomization will be performed.*
* *Outlier criteria: Please describe predefined outlier criteria that would lead to exclusion of animals or data points.*
* *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.*

# INTERVENTION AND EXPERIMENTAL PROCEDURES

*For each study group including controls, please describe[[2]](#footnote-2) and give rationale*

* *How the interventions / procedures are to be carried out. Give details on e.g. drug formulation and dose, availability of the drug formulation, site and route of administration, surgical procedure, anaesthesia, provide details of specialist equipment to be used and suppliers*
* *When: e.g. time of day*
* *Where: e.g. lab, cage*
* *By whom*

*Illustrate your intervention scheme graphically.*

# SAMPLE SIZE CALCULATIONS AND STATISTICAL ANALYSIS

## Proposed sample size / power calculations

*Please substantiate:*

* *What is the experimental unit of your study (see* [*glossary*](https://projekttraeger.dlr.de/media/gesundheit/GF/Glossary_preclinical_studies_2022.pdf)*)? Clearly outline independence / dependence of experimental units (and nesting, if applicable).*
* *What is the minimum clinically relevant effect size based on the previous results that is planned to be achieved with this confirmatory study? (Data need to be publicly available. If not, confidential reports summarizing the data have to be submitted with the application.)*
* *What is the proposed sample size? It must be based on the experimental unit. Sample size estimation needs to account for larger biological variability in the results of the confirmatory study compared to exploratory experiments. The minimum power for the confirmatory study should be 80%. Include a comprehensible, checkable description of the power calculations and sample sizes detailing the primary outcome measure on which these have been based for both control and experimental groups, as appropriate. It is important that the sample size calculations consider anticipated rates of losses. Please also mention the software used. In case of complex calculations, details on the methods (including references) should be provided.*

## Feasibility

*What is the evidence that the intended sample size is achievable?*

*Comment on the access to animals / cells / samples in labs of partner institutions.*

*Please specify and justify how the experimental units will be distributed across the labs of the partner institutions (multi-centre study).*

## Statistical Analysis

*What is the strategy of statistical analysis? What is the strategy for analysing the primary outcome? If applicable, how will multiple primary endpoints be analysed statistically? Are there any subgroup analyses? How will missing data and subjects withdrawn from the study be handled statistically? How will nesting / clustering, if applicable, be dealt with statistically? How is the multi-centre structure reflected in the analysis strategy?*

# QUALITY CONTROL

*What are the measures for quality assurance? Which institution will be responsible? Which SOPs will be set up / utilized? How will monitoring be conducted? Which precautions will be planned to secure validity of test procedures (also across labs), authentication of substances and biological resources (animals, cells, antibodies, media etc.), skills needed, standardized protocols, (pre-) registration of the study and study protocol.*

# STUDY ORGANIZATION

*Describe the study structure and distribution of work in more detail:*

## Management

* *Describe your strategy for the management of the study/research project.*
* *State the roles and responsibilities of the partners of the study (e.g. coordinating investigator, statistics, performance of the study and adherence to the protocol, quality control).*

## Work packages of partners

*Describe the work packages of each partner.*

## Time flow and milestones

*Describe the proposed time flow with all relevant steps including milestones. Please provide a diagram reflecting preparation (including study protocol, submission to authorities, SOPs, initiation of labs), execution of study, data base cleaning, data analysis.*

# DISSEMINATION / EXPLOITATION

* *Describe your dissemination strategy, especially beyond journal publications.*
* *How will the results be exploited? How will your results facilitate translation of the initial findings into improved therapies? What will be the next steps? In case new evidence will be generated that goes beyond a confirmation, please describe. Please state how the expected results will inform the decision to start clinical (human) trials.*
* *Please describe any potential commercial interest of a company in the results of the study. State your situation regarding scientific and commercial freedom to operate to use the project results.*

# REFERENCES

# FINANCIAL DETAILS OF THE STUDY

## Financial overview and justification

* *Please provide an overview of the study’s finances for the total duration of the study. (1) Justify the planned expenditures (personnel, consumables, overhead, etc.) as running text (here under number 12.1) and (2) fill out the table below. Indicate the total duration of the study. Please make sure that all overhead costs and if applicable, the added value tax (Mehrwertsteuer) for commissions are properly considered.*
* *International collaborations: If the proposed study includes foreign centres or collaboration with organizations in other countries please give full details of funding arrangements agreed or under consideration.*

## 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 study).*
* *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 scientific and commercial exploitation of the results. A statement giving such assurances will be demanded by the funder after the review process is finished.*

*Please do not make any binding agreements before notion of award has been made; please contact the project management agency (DLR-PT) first.**Appropriate agreements on intellectual property, confidentiality, publication of results, property rights must be concluded between all those playing a part in the conduct of the study before start of the study.*

## Other funding

*In case you have already submitted the same request for financial support or parts hereof to other institutions or the BMBF, please mention this here.*

*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 DLR Project Management Agency immediately".

|  |
| --- |
| **Financial table - Acronym** |
| Partner, Task | Institution | Personnel  | Consuma-bles € | Study drug€ | Equipment € | Commissions (incl. tax)€ | Travel€2 | Publication costs€ | Other€ | Over-heads€3 | **Total****funding requested€4,5** |
| Number of Sci, Grad, T, O1 | No. of Person Months | € |
|  *e.g. Coordinating investigator, Project planning and management* | *e.g. University of…* | *e. g. 1 Sci* | *e. g. 24* |  | *e.g. lab expenses* |  | *> 410 €* |  |  | *Only for open access publications*  | *e.g. animal costs, data manage-ment* |  |  |
| *e.g. Study statistician, independent analysis* |  |  |  |  |  |  |  |  |  |  |  |  |  |
| *……* |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Requested Budget****(Sum)** |  |  |  |  |  |  |  |  |  |  |  |  |  |

**1**Sci = Scientist, Grad = Graduate student, T = Technician, O = Other; Please calculate your local institutional salaries.

2flat-rate: up to 1.500€ per full time scientist/graduate student per year

**3**Overhead = Gemeinkosten, 20% Projektpauschale

**4**Please calculate requested amount according to funding rate: generally up to 100% of total costs for academia

5Please summarize for each institution

# APPENDICES

*The following documents have to be submitted with the full proposal (full proposal and attachments as one pdf document). The appendices are to complement the information given in the respective sections of the study description.*

## 1 GRAPHIC STUDY OVERVIEW

*Please provide a flow chart of the planned study. Illustrate also the timeline and which work will be done by the individual laboratories (max. one page).*

## 2 DATA MANAGEMENT PLAN

*The data management plan (DMP) is intended to be a living document in which information can be made available on a finer level of granularity through updates as the implementation of the project progresses and when significant changes occur.*

*Please use the table provided below to describe your DMP, which has to ensure data management, maintenance and long-term accessibility for future reuse of your results (also by third parties, considering privacy rules and proprietary data). Also mention at which stage data sharing will be envisaged. To ensure that your research data are soundly managed please follow the principles of FAIR data (https://www.go-fair.org/fair-principles/). Please use existing international standards and data repositories which allow publishing of FAIR data and are non-commercial.*

*Data management costs are eligible for funding during the period of funding.*

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|  |  |
| --- | --- |
| **A** | **General information** |
| A.1 | Acronym |  |
| A.2. | Responsibilites:* data management
* metadata creation
* data security
* quality assurance of data
 | *Apart from the PI: who is responsible*  |
| A.3. | Data management (DM) support office:  | *Is there a DM support office in your institution?*[ ]  Yes [ ]  No*If yes, have you contacted it for support?* |
| **B** | **Description of data set** |
| B.1. | Data to be collected / generated: | *Describe the data that will be collected / generated within the project.* |
| B.2 | Type and format of data: | *Specify the type, and format of the data.* |
| **C** | **Data storage** |
|  | **During the research** |
| C.1 | Volume of data and site of storage: | *What is the volume of the data and where will the data be stored? Is there sufficient storage capacity during the project?* |
| C. 2 | Data back-up and responsibility: | *Will the data be backed-up regularly during the project?*[ ]  Yes [ ]  No*Who is responsible for this?* |
|  | **After the research** |
| C.3 | Trusted Repository and FAIR principles:  | *Specify in which trusted repository the data will be stored after the project[[3]](#footnote-3).**If the data will not be stored in a trusted repository: how will the data be made**- findable,* *- accessible and* *- reusable?* |
| C.4 | Persistent identifier: | *Will a persistent identifier be used to make the data findable?*[ ]  Yes [ ]  No |
| C.5 | Storage of confidential, privacy-sensitive or competition-sensitive data[[4]](#footnote-4): | *How will confidential, privacy-sensitive or competition-sensitive data be stored?* |
| C.6 | Duration of archiving:  | *For how long will the data be archived?* |
| **D** | **Standards and metadata** |
| D.1 | Documentation of data: Metadata standard: | *How will the data be documented?* *What metadata standard will be used to make the data accessible and reusable? If no standard exists please outline how a suitable metadata structure will be developed.*  |
| **E** | **Making data available** |
| E.1 | Availability / reuse of the data:  | *Are the data available for reuse after the project?*[ ]  Yes, immediately after the project [ ]  Yes, after ....months/years [ ]  No*If not, please explain why the data are not suitable and/or available for reuse.* |
| E.2 | Limited availability of data? | *If data are only made available after a certain period then please state the reason for this.* *If part of the data cannot be made (directly) available then please state the part concerned.* |
| E.3 | Conditions for the reuse of the data  | *Please specify:**If so, are/will these conditions (be) defined in a consortium agreement?* |

## 3 DECLARATION OF PARTNERS INVOLVED IN THE STUDY

The signatures of the participating laboratories indicate that the signees agree to participate in the preclinical study [acronym] and support the study as described above.

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

|  |
| --- |
| **Study acronym:** |
| **Coordinating investigator** |
| # | Name | Affiliation | Responsibility / Role | Signature |
|  |  |  |  |  |
| **Study statistician+** |
| # | Name | Affiliation | Responsibility / Role | Signature |
|  |  |  |  |  |
| **Data Management** |
| # | Name | Affiliation | Responsibility / Role | Signature |
|  |  |  |  |  |
| **Participating Laboratories** |
| # | Name | Affiliation | Responsibility / Role | Signature |
|  |  |  |  |  |
|  |  |  |  |  |
| **Supporting Facilities** |
| # | Name | Affiliation | Responsibility / Role | Signature |
|  |  |  |  |  |

+ The study statistician needs to be qualified. In the CV, evidence should be provided, e.g. certificate of GMDS / IBS-DR. s

CVs of major participants

## 4 CV OF MAJOR PARTICIPANTS

*Indicate the preclinical study expertise of the major participants. Include tabular scientific CVs (max. one page) for academic members of the study team playing a leading role (i.e. coordinating investigator, co-applicants, study statistician, data manager, not all collaborating partners at all sites) including a list of a maximum of 5 publications of the last 5 years (related to the planned study).*

1. *In preparation of the proposal the following information related to study design is worth noting:*

[Handreichung DECIDE](https://www.bihealth.org/fileadmin/QUEST/Publikationen/Bericht/DECIDE_Guidance_for_planning_and_conducting_confirmatory_preclinical_studies_and_systematic_reviews.pdf)

<https://www.nc3rs.org.uk/our-portfolio/experimental-design-assistant-eda>

<https://journals.sagepub.com/doi/10.1177/0023677217724823>

<https://www.nc3rs.org.uk/arrive-guidelines>

 [↑](#footnote-ref-1)
2. *You may find recommendations for a description in the TIDieR checklist and guide*. [↑](#footnote-ref-2)
3. See for example: <https://www.publisso.de/forschungsdatenmanagement/publizieren/publisso-repository-finder>

 or <https://www.re3data.org/> https://www.publisso.de/open-access-publizieren/forschungsdaten/forschungsdatenrepositorien/https://www.publisso.de/open-access-publizieren/forschungsdaten/forschungsdatenrepositorien/ [↑](#footnote-ref-3)
4. This section MUST be completed if your research data includes personal data relating to human participants in research. For other research, the safeguarding and security of data should also be considered. Please note this section concerns protecting the data, not the patients. [↑](#footnote-ref-4)