**Outline Application – Preclinical Confirmatory Study (Module 1)**

*To ensure comparability of all submitted outline applications please prepare your application in English* ***not exceeding 8 pages*** *(DIN A4, at least 11 point Arial and 10 point Arial for the synopsis and references, margins of at least 2 cm and single-spaced lines).*

*Structure your application using the headings listed below. Make an entry under each heading/subheading. Please replace the italicized text with your information.[[1]](#footnote-1)*

*Additionally, 3 appendices are to be submitted (one page each). Appendix 3:* ***Signatures*** *of the coordinator, PIs and statistician to confirm that the information and data given in the outline application are correct.* ***Do not*** *submit any other appendices.*

**STUDY SYNOPSIS**

|  |  |
| --- | --- |
| **COORDINATING INVESTIGATOR** | *Name, address, telephone, e-mail* |
| **PARTICIPATING LABS** | *To be involved (n):*  *Name of PI, Affiliation, City* |
| **TITLE OF STUDY** | *Descriptive title, max. 140 characters. In case of funding this title shall be quoted in the annual reports of the BMBF.* |
| **ACRONYM** | *Derived from the title, max. 40 characters* |
| **Time Scale** | *Duration of the entire study (months)* |
| **Budget applied for** | *Please give the total amount for the consortium* |
| **Medical Field** | *Please name the medical field(s) the study addresses* |
| **MEDICAL CONDITION** | *Please describe the medical condition addressed* |
| **OBJECTIVE(S)** | *Which hypothesis is to be tested? Specify the primary objective of the study that determines sample size calculation. Specify any secondary objectives.* |
| **Model/SETTING** | *Animals/strain, probes/samples of humans, cultured cells, etc. to be used* |
| **INTERVENTION** | *Please describe shortly:*  *Intervention:*  *Control intervention (pos./neg.):* |
| **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* * *Outcome: define the primary efficacy endpoint; key secondary endpoint(s)* * *Methods to reduce risk of bias: randomization and blinding* |
| **Statistical planning and  analysis** | *• Shorty outline the sample size calculation (including rationale for the chosen effect size and statistical power). Motivate this by effect sizes from previous studies.*  *• Indicate the total number of animals / cultured cells / samples to be used in each experiment, and the number of animals / cultured cells / samples in each experimental group*  *• Shortly outline the statistical methods to be used for each analysis* |

***Graphic study overview:*** *Please illustrate the study graphically with a flow chart in appendix 1 including at least the aspects: objective, setting, intervention and study design (e. g. using the experimental design assistant EDA,* [*https://eda.nc3rs.org.uk*](https://eda.nc3rs.org.uk)*). Illustrate also the timeline of the study.*

*Below, please substantiate and justify:*

**1. RELEVANCE**

### Clinical Relevance and Novelty

* *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 and relevance for the treatment of the disease of the proposed study?*

**Impact of the study**

* *Please describe possible results and impact of the planned study.*
* *What will be the next steps?*

**2. SCIENTIFIC PREMISE / PREVIOUS RESULTS**

*This section should detail the background of the study hypothesis.*

**Scientific premise**:

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

* *Please describe how the existing literature was systematically reviewed to avoid duplication of research. Provide your search strategy (data bases, search terms, operators, filters; time period covered; date of search) and results.*
* *A full electronic search strategy exemplary for one database, including any limits used, has to be presented in appendix 2 (max. one page). Guidance concerning search techniques can be found at the following address:* <https://www.camarades.de/systematic-search.html>

**Previous (own) results directly related to the planned study**:

* *Please describe previous results, e.g. explorative studies, triangulation, within-lab replication, 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.*
* *Describe and justify deviations between your previous study and the planned confirmatory study.*

***It is strongly recommended*** *to check the minimum requirements to start a confirmatory study in the* [*guidance document of the DECIDE project*](https://www.bihealth.org/fileadmin/QUEST/Publikationen/Bericht/DECIDE_Guidance_for_planning_and_conducting_confirmatory_preclinical_studies_and_systematic_reviews.pdf)*.*

***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 of the DECIDE project*](https://www.bihealth.org/fileadmin/QUEST/Publikationen/Bericht/DECIDE_Guidance_for_planning_and_conducting_confirmatory_preclinical_studies_and_systematic_reviews.pdf)*.*

**3. RELEVANCE OF THE MODEL**

*Which model is to be used? Please provide details for animal species and strain / cell model, source of animals or cells, age and sex.*

*Please provide sound scientific reasoning why the chosen model can address the scientific objectives and its relevance to the human disease. Please also state limitations of the model.*

*In case animal studies are planned please explain:*

* + *why there are no realistic non-animal alternatives*
  + *Is the (animal)model different from the previous/to be confirmed studies? If yes, why?*

**4. STUDY DESIGN**

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

### CONTROL(S) / COMPARATOR(S)

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

### INCLUSION / EXCLUSION CRITERIA

*Justify the inclusion and exclusion criteria, the population to be studied, include reflections on generalizability and representativeness (external validity, age, sex, comorbidities).*

### INTERVENTION(S)

*Justify the choice of your planned intervention(s)/treatment(s).*

*Define the primary outcome. It should be the same (or similar) as in the exploratory study. Secondary outcome measures can serve as supporting evidence.*

*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.*

*Describe:*

* + *Method for randomization*
  + *Procedures for blinding*

*If randomization or blinding is not possible please explain why and give details of alternative methods to avoid biased assessment of results.*

**5. STATISTICS**

**5.1 PROPOSED SAMPLE SIZE / POWER CALCULATIONS**

*Justify:*

* *What is the experimental unit of your study (see* [glossary](http://www.dlr.de/pt/Portaldata/45/Resources/Dokumente/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?*
* *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 in the confirmatory compared to the 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 will take into account anticipated rates of losses.*

**5.2 Statistical Analysis**

*Please describe:*

* *What is the strategy of statistical analysis? What is the strategy for analyzing the primary outcome? Are there any subgroup analyses?*
* *How does the analysis parallel/deviate analysis strategies from the studies that are to be confirmed?*

*Please explain: how will you define if the confirmation of your study has been successful or not?*

**6. QUALITY CONTROL**

*Please describe shortly the strategy for harmonization of protocols as well as trainings between different labs.*

*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, independence of data analysis and monitoring.*

*Please keep in mind and plan accordingly: in the full proposal stage you will have to give details on data management, maintenance and long-term accessibility for future reuse of your results (also by third parties, respecting privacy rules and proprietary data).*

*To ensure that your research data are soundly managed please follow the principle of FAIR data[[2]](#footnote-2). Please use existing standards and data repositories.*

**7. ETHICAL CONSIDERATIONS**

*If applicable:*

*Discuss briefly the acceptability of the harm incurred by the animals versus the potential benefit for the patients.*

**8. STUDY MANAGEMENT**

### MAJOR PARTICIPANTS

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

|  |  |  |  |
| --- | --- | --- | --- |
| **#** | **Name** | **Affiliation** | **Responsibility/Role** |
|  |  |  | *Principal/Coordinating Investigator* |
|  |  |  | *Participating lab* |
|  |  |  | *Statistician (study planning and analysis)* |
|  |  |  | *Data management* |
|  |  |  | …… |

### STUDY EXPERTISE

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

**9. REFERENCES**

**10. FINANCIAL SUMMARY**

*Please give a rough estimation of the costs expected for the total duration of the study showing the overall financial structure of the project. Please make sure that all overhead costs (e.g., “Projektpauschale” for universities and university clinics) are properly considered. Inclusion of overhead costs must be clearly visible. In addition, also consider the added value tax (Mehrwertsteuer) for commissions, if applicable. An additional justification of the costs is not required at this stage.*

|  |  |
| --- | --- |
| **Item** | **Costs (€)** |
| *Personnel (position, task)* |  |
| *e.g. PI / Project Management* |  |
| *Scientists (e.g. study design, study execution, biostatistical planning and analysis, documentation and data management, quality assurance, cooperation with the accompanying research project)* |  |
| *Technicians* |  |
| *Materials (e.g. consumables, lab expenses)* |  |
| *Equipment (> 410 €)* |  |
| *Commissions (incl. 19 % tax)* |  |
| *Travel (e.g. lab visits, meetings)* |  |
| *Other (e.g. animal costs)* |  |
| **Total Budget** |  |
| **Institutional Overhead***: e.g. 20% “Projektpauschale” for universities / university clinics* |  |
| **Requested Budget (Sum)** |  |

**APPENDICES**

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

### STUDY OVERVIEW

*Please provide a flow chart of the planned study to complement the information given in the study synopsis (e.g. using EDA, see above)*

### SEARCH STRATEGY

*To substantiate the scientific premise presented in section 2, please present the full search strategy for the electronic database including any limits used, such that it could be repeated. Indicate filters used. Present the search strategy only, do not provide further explanations. The narrative of the results is to be presented under section 2. For guidance refer to* [*http://syrf.org.uk/*](http://syrf.org.uk/)

### SIGNATURES

### Project title and acronym:

|  |  |  |  |
| --- | --- | --- | --- |
| Function | Name | Institution/Department | Signature\* |
| Coordinator |  |  |  |
| Statistician |  |  |  |
| Partnering lab PI |  |  |  |
|  |  |  |  |

\*I herewith confirm that all information and data given in the outline application are known to me and correct.

1. *In preparation of the application 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. <http://www.forschungsdaten.org/index.php/FAIR_data_principles> [↑](#footnote-ref-2)