BIH CRU Clinical Research Grant – GUIDE FOR APPLICANTS

Berlin Institute of Health

The Berlin Institute of Health (BIH) supports the development of new diagnostic, therapeutic and preventive procedures that improve human health. In line with this guiding principle, BIH promotes and strengthens inter-institutional collaborations of basic scientists, computational researchers and clinicians from Charité - Universitätsmedizin Berlin and Max Delbrück Center for Molecular Medicine (MDC) that are embedded into translational research projects and apply an overarching systems medicine approach (see paragraph below for general definitions).

Promotion of research by BIH comprises funding of projects and the development of a shared research space between Charité and MDC to create an optimal environment for translational research in the framework of systems medicine. The shared research space includes a Clinical Research Unit (CRU), to facilitate collaboration scientists and clinicians from the pre-clinical research phase to initial clinical studies. In addition, BIH offers its scientists state-of-the-art research infrastructure, such as an Omics Core Facility that provides high-troughput technologies and a Bioinformatics unit to analyze large amounts of data. BIH is also establishing an advanced Medical Imaging Core Facility for clinical phenotyping, a joint BIH Biobank as well as a Stem Cell Core Facility, a Transgenics unit and a BIH Chemical Biology Platform.

Definitions

Translational Research*

At BIH, “translation” stands for a quality-oriented process of transferring knowledge generated in systems medicine-based approaches into medical benefits, as well as observations from clinical practice into basic science. Thus, translation represents an interdisciplinary process encompassing the discovery of mechanisms of action and their development into clinical tests on patients, with the aim of developing new procedures for diagnosis, therapy and the prevention of disease. This process also includes the critical review, further development and revision of established models.

Systems Medicine*

Systems medicine at BIH encompasses methods to analyze the dynamic interactions of vital molecules, cells, tissues and organs as well as psychosocial factors that form the foundations of life, in an effort to develop a broad understanding of the interrelations (systems) that constitute a healthy human organism.

Systems medicine uses mathematical modeling to integrate data derived from clinical and experimental research to decipher the influence of different parameters (genetics, epigenetics,

metabolism, infection, lifestyle and environment) on the human organism and to use this knowledge to conduct more precise studies. Systems medicine integrates and structures this complex information for a better understanding of the etiology, development and progression of disease and in the development of diagnostic, therapeutic and preventive procedures.

Exploratory Research

BIH defines exploratory (also known as high-risk) research as initial research conducted on a new idea or concept that is not fully underpinned by scientific evidence. This comprises a new area of research as well as the application of novel approaches and/or a new perspective on "established" research topics. Exploratory projects often comprise pilot or feasibility studies that lay the initial groundwork for future research and have the potential to catalyze rapid and innovative advances.

* Working translation of the German definitions approved by the BIH Directorate on 10 November 2014. The original German version that can be found at the end of this document is binding.

The BIH CRU Clinical Research Grant

BIH has developed the CRU Clinical Research Grant to provide support for science-driven clinical trials and to spark off new scientific collaborations between clinical research and basic science, particularly between Charité - Universitätsmedizin Berlin (Charité) and Max Delbrück Center for Molecular Medicine (MDC) that follow the paradigm of translational and systems medicine.

A primary goal of the funding instrument is to strengthen the BIH/CRU profile and to establish CRU infrastructure. Therefore projects have to contribute to the development of the CRU infrastructure within the BIH and should establish structures or resources, which will support BIH scientists beyond the scope of the individual application. Clinical parts of the funded projects have to be perfomed in the BIH Clinical Research Unit (CRU) and in collaboration with BIH core facilities (CF).

The program supports innovative concepts to facilitate trial associated science. It provides (co)-funding for interventional trials, including pharmacological trials according to AMG, cohort studies, as well as prognostic, diagnostic, and stratification marker trials. This includes first-in-man, pilot, proof-of-mechanism/concept or feasibility studies up to phase IV trials. BIH Clinical Research Call is open to all research areas.

Eligibility and evaluation criteria

BIH CRU Clinical Research Grant brings together clinical research and basic science, preferentially by collaboration between scientists from Charité and MDC. Researchers from Charité and/or MDC who have completed their academic training (a doctorate as a rule) are eligible. Application is possible by a single PI or by a team of investigators. At least one applicant is PI or Co-PI of the proposed clinical trial and has a track record in clinical research.

Application is possible for:

a) clinical trials with Charité or MDC as sponsor (Investigator Initiated Trial (IIT))
b) Additions to ongoing clinical trials (clinical trial associated science)

Funded projects should perform translational research embedded in an overarching systems medicine approach, i.e. they should contribute substantially to the understanding of basic mechanisms of diseases that are not restricted to specific organs and have the potential to deliver solutions to unmet clinical needs. Apart from this general remit, BIH CRU Clinical Research Grant is open for all research areas. BIH particularly invites early career and female researchers, but also basic scientists to apply and encourage applicants to submit research designs based on preliminary (unpublished) work or untested novel ideas.

PIs that are invited to submit a full proposal are expected to have a contract with Charité or MDC for the duration of the proposed work. Alternatively a letter of intent signed by the authorized superior can confirm that the applicant has a secured position for the duration of the proposed project: Charité employees with expiring contracts are asked to provide a letter of intent signed by the Director of the hosting institute or center (i.e. *Kaufmännischer Centrumsleiter*). MDC applicants whose contracts will expire during the proposed funding phase are asked to provide a letter of intent signed by the Scientific Director of the MDC.

If a PI changes the workplace during the application or funding phase, the BIH CRU coordinator needs to be informed immediately to discuss necessary measures.

Evaluation criteria include innovation, relevance to the mission of the BIH, contribution to the improvement of the CRU infrastructure, additional external funding, track record of the applicant, added value resulting from the collaboration between clinical research and basic science, preferentially MDC and Charité, establishment of BIH-cohorts, and added value resulting from central use and operation of BIH core facilities and the CRU.

The promotion of equal opportunities on a structural and personnel level is firmly rooted in the self-understanding of BIH. BIH strives to support a minimum of 25% female PIs. To achieve

this goal, preference will be given to projects with a balanced gender representation if the scientific quality of two or more projects is equal.

Scope and Duration of Funding

BIH (co-)funding is possible for staff, consumables and other costs[1]. For established/senior PIs appropriate own contribution (such as co-funding or institutional support) is expected. A maximum budget of approximately 250,000 € (direct costs) will be granted per project for up to 2 years with no-cost extension possible for another year. Projects with budgets exceeding this amount will have to provide a detailed justification based on available co-funding, expected outcome and contribution to the establishment of CRU infrastructure.

It is envisioned to fund approximately 6 projects in the first funding period.

The granted budget is intended predominantly for personnel, consumables and fees for the CRU and core facilities as requested in the projects budget plan. Other costs (insurance for patients and/or test persons, payments to patients etc.) will be provided to the applicant directly. Funded personnel will be located at the respective CRU site.

Prerequisite for the allocation of personnel, consumables, fees or transfer of other costs is the approval of the study and the accompanying scientific investigations by the authorities applicable to the particular type of study (IRB, central IRB, PEI/BfArM/EMA, LaGeSo) as well as the clinical trial registration at international and BIH/Charité database level and the insurance of the probands/patients.

Application Procedure

The selection process comprises two stages:

Stage 1: Submitting a pre-proposal
In the first stage of the call, applicants are invited to submit a pre-proposal that consists of a short project outline (approx. 2 pages) and a rough timeline and budget plan plus necessary annexes such as publication list and CVs. Necessary forms are available at www.bihealth.org/de/artikel/bih-cru-clinical-research-grant-179/. Deadline for submission at the **BIH online application portal** is 12 August 2015 at 3 pm. You will have to register to use the BIH portal.

[1] such as costs of monitoring, insurance for patients and/or test persons, recruiting costs, costs of supervisory boards (only costs related to the trial may be requested), payments to patients, third party services

During the online application process, you will be asked to provide the following information/documents:

- Applicant details (name, email, department, project role)
- Co-Applicant(s) detail(s) if applicable (name, email, department, project role)
- Short and full title of the proposed clinical trial
- Total funds requested
- Project outline (PDF)
- Budget table (Excel and PDF)
- Milestones/Gantt diagram (PDF)
- CVs for applicant and all co-applicants (PDF)
- Projected use of CRU & Core Facilities (PDF)

Checklist for eligibility

Please make sure to provide all information listed below in accordance with Good Clinical Practice (GCP) and recommendations for "Safeguarding Good Scientific Practice".

Checklist for submission of pre-proposals (1st stage)

- Applicant is PI or Co-PI of the associated clinical trial
- Applicant is employee of Charité or MDC
- Applicant has a PhD or Dr. med. degree
- Applicant with experience in clinical trials2
- Science-driven trial (IIT) or Clinical Trial associated Science
- Description of innovative elements and/or the potential of the project to develop new diagnostic, therapeutic and preventive procedures.
- Proposed Clinical Project fits into the mission of and the general framework of translational research and systems medicine. Expected establishment of BIH-cohorts, and added value resulting from central use and operation of BIH core facilities and the CRU.
- Description of the expected contribution to the improvement of the CRU infrastructure, and added value resulting from the collaboration between clinical research and basic science, preferentially MDC and Charité for BIH scientists beyond the scope of the individual application.
- Overview on study design and rationale including study hypothesis, regulatory aspects, objectives, endpoints and outcome measures
- Sample size considerations (estimated)
- Rough Gantt diagram incl. planned phases of preparation, patient recruitment and follow up
- Rough budget plan for 2 years

[2] proved by track record - publications or PI of registered clinical trials - or for early career researchers at least certified GCP-training

- Established/senior PI provides own contribution
- Description of involvement of early-career/female/basic scientists .
- Overview of the preliminary work and relevant publications

Checklist for submission of full proposals (2nd stage)

- Applicant is PI or Co-PI of the associated clinical trial
- Applicant is employee of Charité or MDC
- Applicant has a PhD or Dr. med. Degree
- All applicants have a secured position (or letter of intent)
- Applicant with experience in clinical trials
- Science-driven trial (IIT) or Clinical Trial associated Science
- Description of innovative elements and/or the potential of the project to develop new diagnostic, therapeutic and preventive procedures.
- Proposed Clinical Project fits into the mission of and the general framework of translational researc systems medicine. Expected establishment of BIH-cohorts, and added value resulting from central u and operation of BIH core facilities and the CRU.
- Description of the expected contribution to the improvement of the CRU infrastructure, and added resulting from the collaboration between clinical research and basic science, preferentially MDC an Charité for BIH scientists beyond the scope of the individual application.
- Description of study design and rationale including study hypothesis, regulatory aspects, objectives, endpoints and outcome measures.
- Description of study population incl. most important selection criteria
- Description of screening/enrolment/ randomization/ blinding procedures including departments an participating institutions beyond Charité and MDC
- Flow chart including assessments of efficacy and safety
- Statistical counselling, description of statistical analysis / sample size calculations
- Plan for data collection and management incl. description of intended IT resources (Electronic Data Capture system etc.)
- Plan for bio-sample management
- Detailed Gantt diagram incl. planned preparation phase, enrolment and follow up period, analyzing reporting phase AND MEASURABLE milestones (including milestones for the interim evaluation afte first year of funding)
- Definition of study stopping rules
- Detailed budget plan for 2 years incl. requested budget for CF- and CRU- activities
- Established/senior PI provides own contribution
- Plan for quality management (monitoring, SAE management, incl. required and intended boards)
- Description of involvement of early-career/female/basic scientists .
- Overview of the preliminary work and relevant publications
- Plan for publications and disclosure of study results
- Signed approval form for CRU
- Signed approval forms for all required CFs

- Approval for clinical trial by all appropriate authorities (IRB, central IRB, PEI, BfArM, EMA, LaGeSo et
  (If no approval is available yet please indicate status of required processes.)
- Approval for animal research (if applicable)
  (If no approval is available yet please indicate status of required processes.)

Stage 2: Submitting a full proposal

Applicants invited to the second stage of the call are asked to submit a full-length project proposal by **12 October 2015 at 3 pm** using the application form that will be provided.

Applicants that are invited to submit a full proposal will receive support from BIH-CRU central services (biostatistics, regulatory affairs, IT, data protection, sample management, and monitoring) to facilitate fast and efficient high-quality submission.

Evaluation Procedure

Stage 1: Review of the pre-proposals

The pre-proposals will be evaluated as follows:

a) Check for eligibility and completeness
b) Check for quality, relevance and feasibility based on the main evaluation criteria by a committee of reviewers from Charité and MDC

To pass the initial screening for eligibility and completeness, please include all information and documents requested in the checklist. Pre-proposals that do not fulfill eligibility criteria will be rejected (you may re-apply to the next call).

Eligible pre-proposals will be checked for quality, emphasizing the translational and systems medicine aspects, novelty and feasibility by a committee of reviewers from Charité and MDC. To ensure an unbiased evaluation, each reviewer will be blinded to the comments and grading of their colleagues. The individual reviews will be consolidated at the BIH head office to provide the basis for a final ranking by the review committee. The reviewers will suggest one internal and one external reviewer for each full proposal. Up to nine pre-proposals will be invited to submit a full proposal.

Stage 2: Review of the full proposals

Full proposals will be evaluated by a team of internal and external reviewers excluding reviewers with conflict of interest. Reviewers will be asked to provide a written evaluation and a score. Evaluation of the pre-proposal and of the full proposal will be considered for the final ranking. Based on the resulting final ranking, the BIH Board of Directors will decide which

research projects will receive BIH funding (approximately six in the first funding period). Applicants will be notified in January 2016. Funding will be available from February 2016 at the earliest.

As budgetary constraints might limit funding of quality projects in a competitive call, full proposals that pass a minimum score but do not receive funding will be invited to re-submit an updated full proposal for the next CRU Clinical Research Grant.

Main evaluation criteria

The review process will focus on the following aspects:

- Implementation of translational research in the framework of systems medicine
- Contribution to the research focus of BIH (Charité, MDC)
- Quality of the proposed research (i.e. feasibility, experimental design, milestones)
- Is the trial clinically relevant?
- Is the clinical trial based on a hypothesis?
- Does the trial have a predefined primary outcome measure?
- Are the study objectives, endpoints and outcome measures clearly defined and divided into primary, secondary and/or exploratory?
- Is the outcome measure suitable to test the hypothesis?
- Innovative or exploratory character of the project
- Potential of the project to contribute to the development of new diagnostic, therapeutic and preventive procedures
- Potential to establish infrastructure for future projects and/or co-operations between basic science and clinical research, particularly between Charité and MDC
- Science-driven clinical trial: Investigator Initiated Trial (IIT) or addition to ongoing clinical trials (Clinical Trial associated Science)
- Involvement of early-career and/or female researchers and clinicians
- PIs' track record and achievements relative to their stage of career
- Appropriateness of the requested budget
- Appropriate measurable and decision relevant milestones (including milestones for the interim evaluation after the first year of funding)
- Proper regulatory categorization of the proposed study (e.g. off-label, PoC study, pharmacological trial according to AMG (phase I/II etc.))
- Appropriateness and status of all necessary approvals and/or applications

Contact

If you have any questions, please contact the CRU coordinator at the BIH head office:

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Annex: German Definitions

Translation

Im BIH steht Translation für den qualitätsorientierten Prozess, der systemmedizinisch generiertes Wissen in medizinischen Nutzen sowie klinische Beobachtungen in die Grundlagenforschung überführt. Translation repräsentiert somit einen Disziplinen-verbindenden Prozess und umfasst die Entdeckung von Wirkprinzipien, auf deren Grundlage neue Verfahren der Diagnostik, Therapie und Prävention entwickelt werden, bis hin zur Erprobung dieser Verfahren an Patienten und Probanden. Dies geschieht auch unter dem Gesichtspunkt, etablierte Ansätze in Frage zu stellen, weiterzuentwickeln oder zu revidieren.

Systemmedizin

Die Systemmedizin des BIH analysiert die dynamischen Wechselwirkungen der dem Leben zu Grunde liegenden Moleküle, Zellen, Gewebe und Organe sowie psychosoziale Faktoren mit dem Ziel, ein umfassendes Verständnis der den menschlichen Organismus ausmachenden Zusammenhänge (Systeme) zu entwickeln.