All information regarding future IHI Call topics is indicative and subject to change. Final information about future IHI Calls will be communicated after approval by the IHI Governing Board.

Topic 1: Expanding translational knowledge in minipigs: a path to reduce and replace non-human primates in non-clinical drug safety assessment

Expected impacts to be achieved by this topic

The EU legislation[1] makes it a legal obligation to replace, reduce and refine use of animals in research, including a specific focus on restricting the use of the non-human primates (NHP) unless scientifically justified. The development of *in vitro* models is still challenging due to complex biological responses in various organ systems following drug-treatment. Therefore, animals are still requested in the safety testing of new drug candidates, and minipigs are a potential non-rodent alternative to the use of NHPs. In addition, there are scientific and technological opportunities to generate more accurate data from animal studies with the potential to reduce the total number of animals used.

Closing the translational knowledge gap, minipigs versus NHPs and humans, will enable the development of new refined and digital research tools, which will contribute to:

- Reducing and replacing the overall number of NHPs in research and refining their use without compromising human safety.
- Improving disease understanding that will open up new research pathways, and enhanced use of non-invasive digital technologies that are potentially applicable to humans.
- Improving sustainability and quality of biomedical Research and Development (R&D) in areas of unmet medical need by ensuring access to well-characterised minipig models in R&D of medical technologies, medical devices, and pharmaceuticals.
- Optimising knowledge sharing between academia, regulatory, small- and large companies to accelerate generation of knowledge and medical innovation.
- Development and validation of non-animal models and approaches based on new translational research data.

Expected outcomes

- Obtain and share biological knowledge of minipigs, thereby facilitating the development of innovative solutions by improving the translational understanding between minipigs *versus* NHPs and humans, including further understanding of the minipig immune system, with the overall aim to replace, reduce and refine the use of animals in drug safety assessment.
- A regulatory pathway for drug safety assessment of biologicals and other novel therapeutic modalities in minipigs with the potential to impact regulatory strategies.

[1] DIRECTIVE 2010/63/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 22 September 2010 on the protection of animals used for scientific purposes; https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32010L0063

- Publicly available databases and software for physiologic, genomic, transcriptomic, metabolomic, proteomic and epigenetic minipig data to understand underlying mechanisms of disease/toxicities and find new mode of actions for pharmaceutical intervention.

- Characterized and validated genetically modified minipig models:

  - Genetically modified minipig models based on the CRISPR/CAS inducible gene-editing technology.

  - minipigs with “humanized” immune system components and effectors for biologicals’ testing.

  - Small–sized micropig for efficacy/safety assessment to facilitate compound availability in pharmaceutical R&D.

- Assessment of the utility of the minipig as a relevant toxicology species for immunosafety testing using drugs, which have been tested preclinically and clinically. Assisting and synergizing the already existing translational and regulatory efforts related to immunological safety evaluation. Developing validated antibodies and *in vitro* immunoassays to characterize the immune system and assess immuno-safety of drugs in minipigs.

- Minipig-specific technology for automated study data: validated medical devices, biosensors, algorithms, software, and digital animal housing. Machine learning and Artificial Intelligence (AI)-based tools to monitor abnormalities in behaviour and physiological systems in undisturbed animals.

To ensure long term sustainability, all the obtained interdisciplinary science-based knowledge generated in this proposal will be shared, integrated, digitalised, and published in peer-reviewed journals encouraging industry and academia to develop innovative medical science solutions and technologies, such as scientifically and ethically sound animal models, assays, biomarkers, monitoring devices, biosensors for normal physiological behaviour and algorithms. Based on the close collaboration with regulatory bodies, the generated knowledge in this proposal is further expected to impact regulatory guideline strategies. All outputs will require long term sustainability and maintenance to fulfil the scope of the proposal.

Scope

Challenges

- Increasing need to find alternatives to testing in NHPs in line with EU legislation.

- Lack of knowledge about minipigs in safety assessment to allow de-selection of NHP as second non-rodent species across diverse drug modalities with strong scientific confidence.

- Almost no precedence in minipig use for safety testing of biologicals and novel therapeutic modalities [e.g., oligonucleotides, small interfering RNAs (SiRNAs), crystallizable fragments (Fcs), antigen-binding fragments (Fabs), single-chain variable fragments (scFvs), monoclonal antibodies (mAbs), vaccines, gene-editing and cell-based therapies].

- Lack of public minipig reference “omics” with good quality annotation: Full genome sequencing, in parallel with baseline transcriptomics, proteomics, metabolomics and epigenetic information.

- Lack of “humanized” and genetically modified models available for drug efficacy/safety testing, including genetically modified smaller micropigs to address cases of limited substance supply.

- Significant knowledge gap on the minipig immune system and reduced number of laboratory tools and reagents when compared to other toxicology species (rodent and non-rodent).

- Lack of widespread use of biosensors, medical devices, “intelligent” animal housing for automated data collection and analysis in minipig studies.

Objectives:

The overall objective of this proposal is to characterize the minipig for use in R&D of medical technology, device, and pharmaceutical development. The knowledge generated in this proposal may facilitate innovative health solutions, improve disease understanding and human predictions. The goal is to advance biomedical R&D by generating background scientific data to evaluate if the minipigs could be a viable and feasible alternative to NHP in key therapeutic areas, with a special focus on translatability from minipigs to humans.

Key activities

1. Safety assessment and regulatory aspects of novel therapeutic modalities: Compile and publish historical data in minipig biomedical R&D.

2. Evaluate the translatability of minipigs in human risk assessment following treatment with biologicals and novel therapeutic modalities and discuss future perspectives of the minipigs with regulatory agencies.

3. Minipigs multi-omics: Generate omics reference data (genomics, transcriptomics, proteomics, metabolomics, and epigenetic information) to enable translational research in minipigs.

4. Genetically modified pig models including the micro-pig: Characterise and validate humanized and genetically modified minipig models, including the micropig to generate translatable animal models in drug safety assessment.

5. iPig: Digital technologies, clinical data collection and AI: Create, validate, qualify, and benchmark digital solutions that can objectively measure clinically relevant and functional biomarkers in minipigs for use in preclinical toxicity studies in line with the regulatory agencies’ requirements.

6. Minipig immune system: validate reagents, assays, and biomarkers for immunologic investigations: Conduct investigative studies in minipigs to support their translational significance in immuno-safety assessments and validate reagents/assays.

7. Project management: Compile, digitalise, publish existing and newly produced data.

Why the expected outcomes can only be achieved by an IHI project

Generating and compiling comprehensive and complex biomedical datasets within various therapy areas, some of which will be for AI purposes, require involvement of multidisciplinary skills across several industry sectors (pharmaceuticals, medical technologies, biotech, vaccines, etc.) including Small and Medium-sized Enterprises. Previous examples of precompetitive public-private projects within IMI (Safe-T and E-Transafe) and private multicompany initiatives (such as Biocelerate) demonstrated the value of a neutral broker to facilitate precompetitive sharing of proprietary information. Expanding such collaborations beyond one sector to integrate tools, data and know-how from technology and biotechnology sectors, and joining forces with academic partners from various sectors in unprecedented collaborations requires exploring new precompetitive grounds and calls for this neutral brokerage to continue.

Involvement of regulatory authorities at all stages of this proposal is essential considering the objectives to develop alternatives that can be used to generate data for regulatory purposes. Such close collaboration will contribute to accelerating the development of new knowledge and align validation processes with regulatory requirements, and ultimately, the implementation of new solutions in regulatory practice and their deployment in research practice.

Pre-identified industry consortium and contributing partner(s)

In the spirit of partnership, and to reflect how IHI 2-stage call topics are built upon identified scientific priorities agreed together with a number of proposing industrial beneficiaries, it is envisaged that IHI proposals and projects may allocate a leading role within the consortium to an industrial beneficiary. Within an applicant consortium discussing the full proposal to be submitted for stage 2, it is expected that one of the industrial beneficiaries may become the coordinator or the project leader. Therefore, to facilitate the formation of the final consortium, all beneficiaries are encouraged to discuss the weighting of responsibilities and priorities with regard to such leadership roles. Until such roles are formalised by execution of the Grant Agreement, one of the proposing industrial leaders shall facilitate as project leader an efficient drafting and negotiation of project content and required agreements.

Indicative budget

Due to the global nature of the participating industry partners, it is anticipated that some elements of the contributions will be non-EU/Horizon Europe Associated Countries in-kind contributions.

The indicative in-kind contribution from industry partners may include in-kind contributions to additional activities.

Indicative duration of the action

The proposed project will run in 4 phases (current suggestion):

Phase 1: Evaluation of existing minipig data, develop databases, develop bio sensors and algorithms. Data will be published in peer reviewed journals. Knowledge gaps will be identified, and development of minipig models will be initiated. Molecule selection and investigations for Phase 2 will be planned and slots for the studies will be booked. Duration: 12 Months.

Phase 2: Minipigs will be treated with modalities e.g., oligos, SiRNAs, Fcs, Fabs, scFvs, mAbs, vaccines, gene-editing, and cell-based therapies as an alternative to the current precedence of safety testing in NHPs. Duration: 20 Months.

Phase 3: Biomaterial from the minipig studies in Phase 2 will be distributed to various work package members (iPig, multi-omics, immuno-safety) for further evaluation. Mechanisms and translational aspects will be explored. Duration: 16 Months.

Phase 4: Compile, discuss and distribute new knowledge, database scrutinization, publication in peer reviewed journals, regulatory recommendations, and digital health solutions. Duration: 12 Months.

Proposed project duration, in total: 60 Months.

Contribution of the pre-identified industry consortium <and contributing partners>

The industry consortium and contributing partner expect to contribute to the IHI proposal by providing the following expertise and assets:

- Experimental settings: Drug candidates, drug products, animals including genetically modified animals, animal units, experimental equipment, laboratories.
- Data: access to standard toxicology and clinical safety endpoints, historical data, gene expression, immunosafety biomarkers and assays.
- Expertise: nonclinical expertise, data science, regulatory expertise, immunosafety, “omics” evaluation, disease models, devices.
- Technology: Standard for Exchange of Nonclinical (SEND) databases and SEND visualisation systems, implants, device software.

Applicant consortium

Public partners:

- Database constructors: merging large databases from different sectors (various public and industry partners containing complex biological datasets e.g., genomic, transcriptomic, metabolomic, proteomic and epigenetic data.
- Suppliers of genetically modified minipigs and tissue samples.
- Academic partners developing and validating biomarkers to ensure human translatability.
- Inventors of validated algorithmic tools for machine learning and artificial intelligence to generate automated digital animal housing and predict toxicities in minipig vs. human.
- Inventors of technology for automated study data: validated medical devices, biosensors etc.
- Inventors of validated antibodies and *in vitro* immunoassays to characterize the immune system and assess immunosafety of drugs in minipigs.
- Project administration with experience in public-private partnerships.

Regulatory authorities: Advisors.

Dissemination and exploitation obligations

[To be determined: The specific obligations described in the Conditions of the calls and calls management rules under “Specific conditions on availability, accessibility and affordability” [apply][do not apply].] .