IHI Call Days | Call 9

Liver Safety - From Diversity to Patient Centricity

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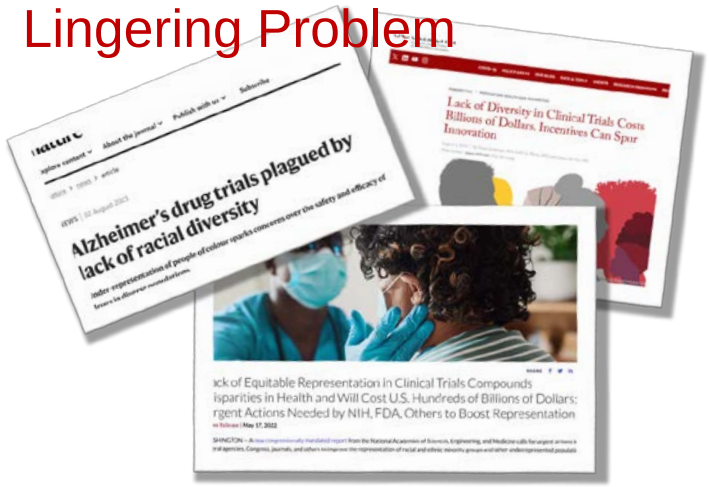
Link to the IHI brokerage platform:

- IHI Call Days - Call 9 (converve.io)

Challenges and objectives

Population underrepresentation in clinical trials with widespread consequences

Lingering Problem



The Clinical Trial Dilemma

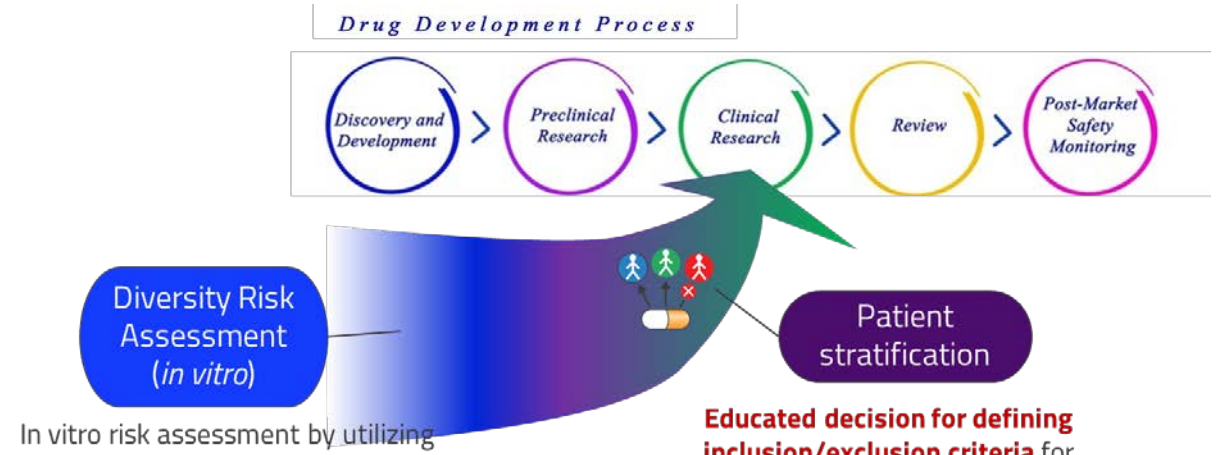
Loose inclusion criteria will put study participants at **unnecessary risk** to experience adverse effects related to individual predisposition

Too stringent inclusion criteria may **obscure important safety information** about use of the investigational drug in patients who will take the drug after approval.

➔ Pre-clinical patient stratification is key !!

Proposed Solution

- Integrate human diversity in pre-clinical development:
  - by applying in vitro panels for safety and efficacy testing
  - which represent major subpopulations by demographic and non-demographic traits



In vitro risk assessment by utilizing human **cell-based assays representing human diversity** for better reflection of underrepresented and vulnerable population

Educated decision for defining inclusion/exclusion criteria for clinical trials supported by *in vitro* data obtained from human diversity panels

Addressing IHI specific objectives: SO2 and SO3

Reflecting Population Diversity in a Dish

Use case: drug-induced liver injury (DILI) – Project Objectives

Diversity determinants and matched traits

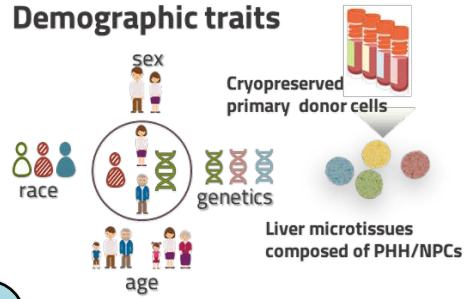
sex/age♂

sex/age♀

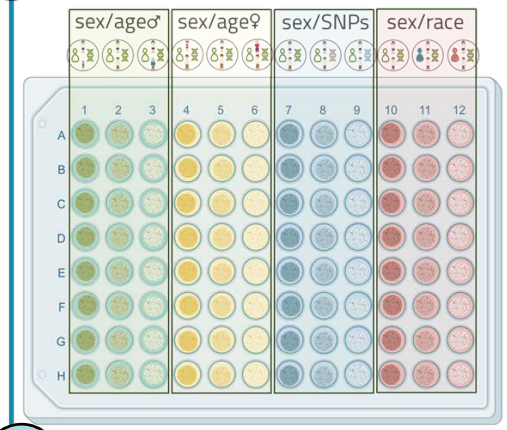
sex/genetic variation

sex/race

Demographic traits

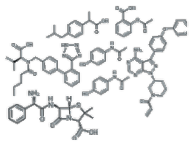


Obj.1 Diversity Test Panel



AI guided Molecular profiling

- Biomarker ID
- Toxicogenomics
- Histopathology

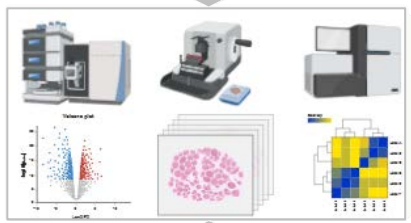


ambigous DILI compounds or IND of clinical DILI cases

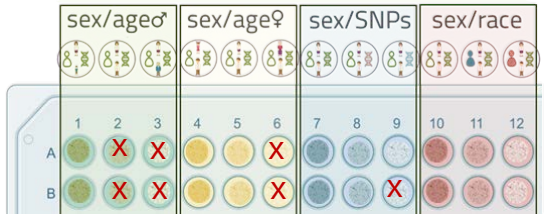
Obj.5 Assay-ready plate cryostorage solution

clinical

x liver biopsies and blood from DILI patients (rare?)



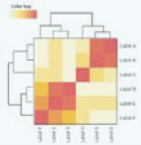
x susceptible donor tissue and medium supernatant



in vitro

Obj.3 Impact of serum components on DILI

Obj.2 Multi-modal correlation analysis with diversity traits



Obj.6
- DILI risk score (3DRS)
- De-risking strategy for pre-clinical and clinical trials.

Obj.7
- Confirm risk avoidance in non-interventional phase 1/2 clinical trials

Obj.4 Vulnerability Test Panel based on donor cells with underlying liver disease

Obj.8 Advanced therapeutic modalities

Obj.9 **POC with iPSC-derived or organoid liver models**

Alternatively, if there is a weak link between diversity factors and DILI, we will consider developing DILI vulnerability panels.

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Is the project suitable for IHI?

- **Why PPP?**
  - Access to diverse expertise across Sectors (Academia, Pharma, Biotech, Patient Organizations, Health care practitioners, Regulatory)
    - Access to real-world data, e.g. proprietary drug development data, historical cases, and access to drug compounds, crucial for validation studies
    - Access to advanced technologies**,** e.g. advanced omics, and screening facilities
    - Access to regulatory insights to ensure developed methods align with regulatory standards, facilitating approval processes
    - Patient centric approaches to integrate patient needs and ensuring clinical relevance
    - Accelerate research transition for sustainable public health impact
    - Resource sharing and enhanced funding without compromising competitive interest

Outcomes and Impact

Expected Results	➢ Diversity/vulnerability panels representing underrepresented demographics ➢ Comprehensive DILI correlation database ➢ Identification of critical biomarkers associated with DILI susceptibility
Expected Outcomes	➢ Enhanced drug safety assessment across diverse populations ➢ Increased inclusivity in clinical trials with better representation ➢ Improved patient stratification for personalized treatment
Expected Impacts	➢ Reduction in adverse drug reactions, especially in underrepresented groups ➢ Accelerated drug development with improved pre-clinical testing methods ➢ Strengthened collaboration between industry, academia, and regulators for future innovations
Solution integration	➢ Integration of clinical data ➢ Engagement with regulators ➢ Pilot studies and validation ➢ Cryotechnology to ensure wider implementation

Outcomes and Impact

Patient benefits	➢ Improved safety by reduce adverse drug reactions, especially for diverse populations ➢ Better patient stratification by identification of DILI susceptibility markers ➢ More inclusive representation of patient subpopulations in clinical trials ➢ Patient-centric approaches help to address real-world needs and concerns
Strengthening EU's Health Industry competitiveness	➢ Innovation Leadership in drug safety innovation through setting new standards for diversity-inclusive drug development. ➢ Accelerating drug development pipelines ➢ Setting new regulatory standards, the project strengthens the EU's role as a global regulatory leader. ➢ Strengthened collaborations through shared resources and expertise

Consortium build up

Core members (so far):

Partner	Sector	Contact	Expertise	in kind
insphero	**Biotech** Schlieren Switzerland	**Wolfgang Moritz** Head of Innovation Management	Advanced 3D in vitro models, service provider for early liver safety, broad customer base in pharma, biotech	✓
Universiteit Leiden The Netherlands LACDR	**Academia** Leiden The Netherlands	**Bob van de Water** LACDR	Expert in in vitro chemical safety assessment and coordinator of large Horizon projects, focusing on innovative drug discovery and safety strategies	✓
livr Cell biology lab VUB VRIJE UNIVERSITEIT BRUSSEL	**Academia** Brussels Belgium	**Leo van Grunsven** Liver Cell biology research group	Expertise, Advanced 3D in vitro models for liver disease, assay development, nucleomics.	✓
UNIVERSITY OF LIVERPOOL	**Academia** Liverpool UK	**Chris Goldring** **Amy Chadwick** Department of Pharmacology and Therapeutics	15 years' experience of evaluation of human models of DILI, multiple IMI programmes, clinical liver research facility	✓
Erasmus MC	**Academia** Rotterdam The Netherlands	**Luc van der Laan** Laboratory of Exp. Transpl. and Intestinal Surgery	Strong focus on translational research in the field of regenerative medicine, organ transplantation, liver disease and liver cancer	✓
UNIVERSITY OF DERBY	**Academia** Derby UK	**Ali Kermanizadeh** College of Science and Engineering	Advanced physiological and pathophysiological in vitro models, particle toxicology, metabolomics, genomics	✓
PredictCan Biotechnologies	**Biotech** Grabels France	**Hong Tuan DUONG** CEO	Advanced 3D cell line-based individual-centric models for drug-induced liver injury and solid cancers. Exploratory mechanistic studies.	✓

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Consortium build up

We are looking for:

Partner	Sector	Expertise/Requirements
	Academia or Pharma	Experienced project coordinator Clinical Hepatologist
	Pharma	Clinical Trial Design Reference compounds Clinical DILI data Biospecimen (e.g. tissue biopsies, blood)
	Academia or Industry	Experts in cryotechnology of living specimens
	Regulatory	Support for alignment of NAM application in pre-clinical testing with current standards
	Patient Organization Health practitioners	Experts in patient advocacy and engagement

Additional information

- Selected scientific references featuring partners' expertise

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Project Objectives

Diversity Platform Development

Objective 2: Correlate liver pathology of clinical DILI cases with patient diversity

Objective 3: Investigate the contribution of systemic, blood-derived factors to drug-related liver adversity

Objective 5: Develop cryopreservation technology for storage and shipment of assay-ready diversity panels

Objective 1: Reflect patient diversity in vitro by representing key demographic and non-demographic characteristics.

Objective 4: Create diversity & vulnerability panels, based on donor cells and sera, for pre-clinical testing, ready to assess and predict the patient susceptibility to drug-induced liver injury (DILI) defined by diversity traits

Option A) Based on diversity donor lots identified to be responsive to ambiguous DILI compounds

Option B) Based on diversity donor lots showing identical/similar pathology to clinical cases

&

Select donor lots with high Diversity-Dependent DILI Score (3DS)

Platform validation

Objective 6:

a) Establish Diversity-Dependent DILI Score (3DS) prediction model based on DILI pathology signatures

b) Develop a Pre-Clinical and Clinical trial DILI De-risking Concept

Objective 7: Confirm risk avoidance in non-interventional phase 1/2 clinical trials by conducting pre-clinical tests using in vitro diversity and susceptibility panels.

Platform extension

Objective 8: Modify test system to effectively evaluate advanced therapeutic modalities

Objective 9: Demonstrate POC for patient centric de-risking based on iPSC-derived or organoid liver models