TransBioLine
Translational Safety Biomarker Pipeline

821283 – TransBioLine

Translational Safety Biomarker Pipeline

WP11 - Communication, dissemination, sustainability

D11.2 Methodology, analysis of existing related initiatives, and tools for implementation

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Document History

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V1.0	21 Nov 2019	First Draft
V2.0	20 Dec 2019	Final Draft
V3.0	08 Jan 2020	Final Document

Definitions

Participants of the TransBioLine Consortium are referred to herein according to the following codes:

UZH. University of Zurich, Switzerland

UMA-IBIMA. Universidad de Málaga, Spain

ITTM. Information Technology for Translational Medicine, Luxembourg

Landspitali. Landspitali University Hospital. Iceland

KUM. Klinikum der Universität München. Germany

UNOTT. The University of Nottingham. United Kingdom

USAL. Universidad de Salamanca. Spain

IR-HSCSP-ICCC. Fundació Privada Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau. Spain

TAM. TAmiRNA GmbH. Austria

SIGNATOPE. SIGNATOPE GmbH. Germany

ABX-CRO. ABX-CRO Advanced Pharmaceutical Services Forschungsgesellschaft mbH. Germany

MetaHeps. MetaHeps GmbH. Germany

APHP. Assistance Publique - Hopitaux de Paris. France

SYNAPSE. Synapse Research Management Partners S.L. Spain

Charité. Charité - Universitätsmedizin Berlin. Germany

UNEW. University of Newcastle Upon Tyne. United Kingdom

ULIV. The University of Liverpool. United Kingdom

MLM. MLM Medical Labs GmbH. Germany

UL. University of Leiden. Netherlands

SAS. Servicio Andaluz de Salud. Spain

PFIZER. LTD PFIZER UK

MSD. Merck Sharp & Dohme Corp. USA & France

LLY. Eli Lilly. USA & UK

NOVARTIS. NOVARTIS Pharma AG. Switzerland

ROCHE. F. Hoffman-La Roche Ltd. Switzerland

Janssen. JANSSEN Pharmaceutica NV. Belgium; U.S.A.

SARD. SANOFI-AVENTIS RECHERCHE & DEVELOPPEMENT. France

Grant Agreement. The agreement signed between the beneficiaries and the IMI JU for the undertaking of the TransBioLine project (No 821283).

Project. The sum of all activities carried out in the framework of the Grant Agreement.

Consortium. The TransBioLine Consortium, comprising the above-mentioned legal entities.

Consortium Agreement. Agreement concluded amongst TransBioLine participants for the implementation of the Grant Agreement. Such an agreement shall not affect the parties' obligations to the Community and/or to one another arising from the Grant Agreement.

Publishable Summary

The aim of this document is to provide an overview of the potential synergies with other initiatives that will be implemented in the project. Also, it provides the methodological framework and sources for the identification of projects or initiatives of relevance for TransBioLine. Details on the current status of interactions established are also given.

1. Introduction

This deliverable aims to report on the contacts and collaborations established with other initiatives in the first months of the project and to present the approach for establishing synergies which is being adopted by the TransBioLine Consortium.

Firstly, the methodological framework that will serve as a continuous reference for the identification of potential collaborations and subsequent development of collaborations will be presented, describing the different steps of this framework. Secondly, the expected synergies of such collaborations will be identified.

Thirdly, the initiatives with which some initial contact has been established are then listed.

2. Methodological framework

The process leading to the identification of synergies and collaboration entails a series of steps that need to be taken into consideration and continuously re-addressed. These refer to collaboration with projects, networks, and other initiatives that are considered relevant for the TransBioLine scope and to be within reach because TransBioLine partners are already involved, and/or collaborations which are already implicitly or explicitly happening.

The process leading to the establishment of collaborations involves five essential steps, that together constitute the methodological framework of reference. The figure below illustrates the workflow for establishing collaborations, highlighting each phase and their interrelation.

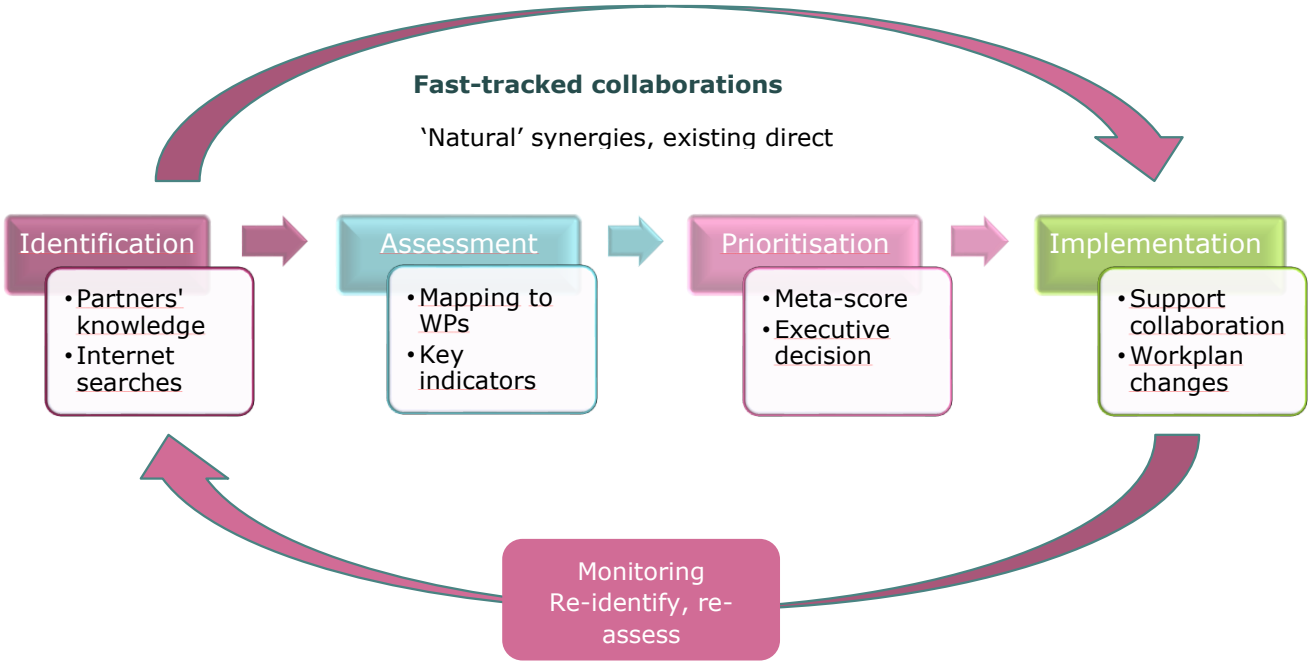

Figure 1: Workflow for the establishment of potential collaborations

The identification and assessment phases have the intention of achieving an overview of the projects and networks located. The whole process, with all its phases, is described in detail below.

2.1 Identification

During this first phase, relevant projects and initiatives are detected and basic information about them is gathered. The main resources for this information are the knowledge of partners, web searches and searches in databases, and spontaneous requests for collaboration received. For each one of the proposals a contact person within the TransBioLine WPs is identified by the Executive Committee as responsible for guiding the collaboration. The consequence of the identification step includes basic information on the project, followed by a pre-review of the partner who suggested the potential initiative (e.g. areas of potential interests overlap, specific results, etc.). Some of the projects can be labelled as 'fast-track'– these are proposals with which collaboration can be easily established due to common intervening stakeholders, obvious benefit, etc. Fast-track projects frequently go directly to the implementation step. For most of these projects, main relations within TransBioLine have been already recognized (usually, the leader and key partners of the most relevant WP, or common partners with the external initiative in question).

2.2. Assessment

The information assembled during the identification phase is then assessed against qualitative/quantitative indicators, such as:

- Technical relevance: results of interest, relevant technologies, WPs most affected, etc.
- Expected impact on project: value for the project, e.g. increased visibility, access to data, saving in time/costs, adding value, etc.
- Viability: technical requirements, timelines alignment, approvals needed, etc.
- Resources: needed to implement cooperation (human, infrastructural, expertise, financial, etc.)
- IPR: rights attached to results of interest, and ownership if known
- Terms: terms for collaboration to happen (e.g. exchange of data, licensing, etc.)
- Legal form: preferred legal instrument for formalisation of collaboration (MoU, or other)

Not all information is known or collected at this point, but this step should try to compile the critical information needed for prioritisation and for establishing synergies.

Assessment of relevance includes indexing according to specific terms, and/or mappings to WPs objectives and tasks. A visual synergy map and their proximity/relevance to TransBioLine project objectives and tasks may be created. For this assessment, indicators may also include qualitative assessment based on the judgement of the partners. Completion of this assessment may require early interactions with the external projects/initiatives. WP11 leaders together with the Executive Committee will be responsible of the assessment.

2.3. Prioritisation

Depending on the project's strategy, needs and preferences, projects/initiatives are organized according to one or more indicators. Projects may also be classified according to different standards in this step, which essentially is about exploiting the information collected in the assessment phase to pick which projects go forward to implementation, and when. This might require some form of executive decision (typically at the Steering Committee level after a recommendation made by Executive Committee).

2.4. Implementation

This step requires the enabling of the collaboration, which can include a wide variety of actions depending on the needs and factors influencing the collaboration, the issues raised, etc. These can be as diverse as, e.g. helping negotiate and sign MoU/agreements/contracts, instigating and formalising changes in the work plan with the additional tasks needed (via new task forces if relevant), supporting the WP leaders and partners in effectively technically establishing the collaboration, addressing Intellectual Property rights (IPR), etc. It does not mean to carry out the work agreed as

part of the collaboration per se but clarifying and facilitating it instead. It typically would also include the progressive creation of a 'toolbox' (templates, financial sheets, communication materials, summary of IPR conditions applicable to the own project, etc.) to aid in the establishment of the collaboration.

2.5. Monitoring

This phase requires the constant follow-up of collaborations, including re-identification (e.g. for projects or results closely related to those already identified, or for fine-tuning preliminary identification), reassessment and re-prioritisation, as needed. This step would also ideally include evaluation in terms of impact of the collaborations implemented, at least on the own project.

3. Potential levels of synergy

Several levels of synergies can be built according with the structure of TransBioLine:

- **Strategic alignment**: High-level interactions can offer a framework for collaboration, in which projects are mutually and regularly followed up, overlaps are detected, incentives for collaboration are created and joint programming is enabled. This can happen through joint meetings or mutual invitations and may also affect the strategic direction of external projects.
- **Outcome utilisation:** Deliverables and results from other initiatives can be shared, re-used, leveraged or exchanged to accelerate progress and to promote program effectiveness. This would typically happen at the WP or task level.
- **Joint work:** Ideally, collaborations would reach a stage at which joint actual work is performed, for mutual benefit, towards the creation of knowledge and results that exceed the original work plan. This happens typically in the most effective manner through the creation of joint, cross-project task forces. Extending goals through collaboration can multiply the impact of projects and create long-term relationships, providing an unparalleled thrust to the respective teams.

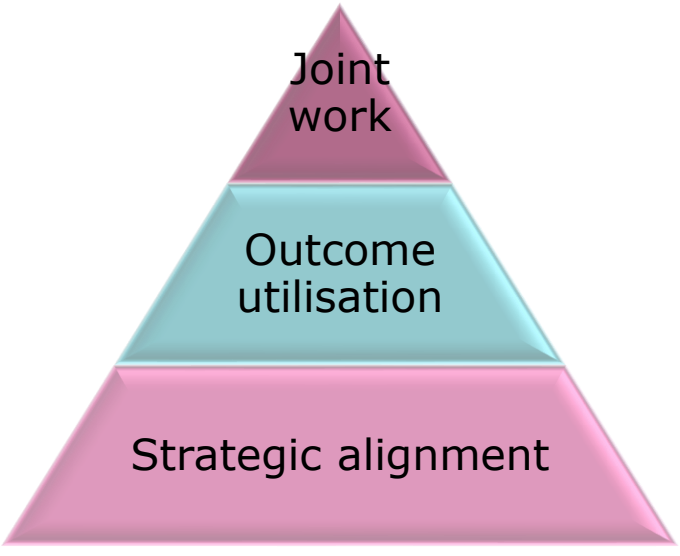

Figure 2. Levels of synergy

These three levels at which collaborations and synergies can happen are described in Figure 2. Naturally, strategic alignment results in recommendations for outcome utilisation; this can easily be the basis for a deeper mutual knowledge, help detect common gaps, and therefore trigger joint work plans.

4. Projects, networks and initiatives for collaboration

An initial list of neighbouring projects and initiatives was cited in the Description of Action (DoA), where mutual interest is described and detailed below in an executive manner:

Initiative/Project	Keywords	Mutual interest	Expected synergy level	TransBioLine WPs involved
SAFE-T www.imi-safe-t.eu (finished initiative)	- Drug-induced kidney, liver and vascular injury - Metabolomics data - Immuno and haematology related biomarkers	- New translational safety biomarkers that will allow the identification and management of side effects of drugs throughout drug development helping to reduce the risk of developing medicines and improving the safety management of patients	Outcome utilization	WP1,2,3,4,5,7,8
Pro-Euro-DILI-Network https://proeurodilinet.eu/about-us	- European registry of prospective drug-induced liver injury cases - DILI specific biomarkers - Liver Injury, Registry, multicentre, phenotyping	- Creation of a multicentre and multidisciplinary European registry of prospective drug-induced liver injury cases	Joint work	WP2, WP6
i2b2 tranSMART Foundation https://transmartfoundation.org/about-us/	- Data analysis - Analysis of clinical, translational and genomics data	- Implementation of systems biology tools to explore miRNA signatures in the context of biological pathways and disease	Joint work	WP6, WP8

Initiative/Project	Keywords	Mutual interest	Expected synergy level	TransBioLine WPs involved
	- Open source - Open-data knowledge management platform	mechanisms in the tranSMART system - Normal healthy volunteer (NHV) reference value dataset uploaded into ITTMs TranSMART system and available to the entire consortium.		
CIOMS DILI working group https://cioms.ch/working_groups/dili/	- Consensus-based recommendations on DILI - Working group with key stakeholders	- To capitalize on existing initiatives in order to provide output that is as comprehensive as possible, does not duplicate other efforts and has added value.	Strategic Alignment	WP2
IMI LITMUS https://litmus-project.eu/	- Liver research - Non-Alcoholic Fatty Liver Disease (NAFLD) - Testing Marker Utility in Steatohepatitis (LITMUS) - Validation and qualification of better biomarkers for testing NAFLD	- To develop, robustly validate and advance towards regulatory qualification biomarkers in liver disease including DILI	Knowledge and tools for biomarker validation and qualification.	WP2, WP6
BBMRI-ERIC Consortium http://www.bbmri-eric.eu/	- European research infrastructure for biobanking	- Creation of long-standing and sustainable biobanks to ultimately to boost biomedical research	Strategic alignment	WP7
EUToxRisk www.eu-toxrisk.eu	-Mechanism-based toxicity assessment - Cell biology, omics technologies, systems biology and computational modelling	- Team with EUToxRisk for the mechanistic and molecular understanding of cellular toxicity of drugs as well as drug-target interactions.	Strategic alignment	WP6
eTRANSAFE	- Integrative data infrastructure and innovative	- eTRANSAFE is investigating novel biomarkers in	Outcome utilization	WP1,2,3,4,5,6,7,8,10

Initiative/Project	Keywords	Mutual interest	Expected synergy level	TransBioLine WPs involved
https://etransafe.eu/	computational methods and tools to improve translational safety assessment during the drug development process	preclinical species, whereas TransBioLine focuses on clinical assessment and qualification. A strong link between both consortia will facilitate translational assessment and help to understand predictive value of new markers, bridging preclinical to clinical safety assessment.		
TransQST transqst.org	-Translational quantitative systems-based toxicological models	-Drug safety -Risk assessment -Translational knowledge (preclinical to clinical)	Strategic alignment	WP7,8,10
C-PATH/PSTC https://c-path.org/programs/pstc/	- Assessment and validation of drug safety tests	-Data sharing - Contributing to further development of evidentiary criteria for biomarker qualification	Joint work	WP10
FNIH's Biomarkers Consortium https://fnih.org/what-we-do/biomarkers-consortium/about	- regulatory approval for biological markers (biomarkers) to support new drug development, preventative medicine and medical diagnostics	- Contribut-inge to further development of evidentiary criteria for biomarker qualification	Strategic alignment	WP10

Since the start of the TransBioLine project, some of the projects initially identified have already been finalised, but other projects have been newly added to the list. Next section describes the already initiated contacts and collaborations.

5. Status of contacts and collaborations

This section describes the progress made with each initiative and project identified.

5.1 SAFE-T

IMI SAFE-T project finished in 2015, before the actual start of TransBioLine. However, the nature and relation of both projects, with numerous common partners and interest, require a specific task in the project in order to enable the use of the SAFE-T assets within TransBioLine.

SAFE-T samples are a major asset for TransBioLine. Access to Quality Control samples comprising the protein biomarkers at high medium and low level will be needed in the TransBioLine project for the following reasons:

a) For assay validation. That means testing an established assay under routine conditions.

b) For study-validation. Testing Biological QC samples should be included in every assay batch to control the performance of the assays in the course of the project.

Additionally, the consortium wants to use as much as possible the data stored on SAFE-T's tranSMART database.

Ultimately, we aim at transferring and incorporating the urinary and blood samples with informed consent allowing use outside and beyond the original consortium, into the Charité Biobank "ZeBanC", in order to establish a unique and comprehensive repository. Those samples would complement the foreseen sample acquisition of TransBioline leading to a more robust analysis and qualification.

Contacts are currently in place with the SAFE-T Sample Repository at Consorci Institut Català de Ciències Cardiovasculars (ICCC) in Barcelona and the former recruiting sites of SAFE-T (together with the corresponding sites' IRB's) in order to pursue the transfer of the SAFE-T samples in a way that the abovementioned integration is ethically acceptable.

5.2 Pro-Euro-DILI-Network

The main aim of the PRO-EURO-DILI-NET COST Action is to set up a European-wide interdisciplinary co-operative network of stakeholders in the DILI field (including scientists, clinicians, regulatory authorities, Small and Medium Enterprises (SMEs) and industry partners). Through workshops, scientific exchanges as well as training schools, this Action coordinates the efforts aiming to advance the understanding of DILI as well as facilitate the translation of basic research and preclinical findings into clinical practice.

The collaboration with the Pro-Euro-DILI-Network will facilitate enrolment of well-characterized patients with DILI and appropriate disease controls, with linked biological samples, as well as provide an established expert panel to adjudicate cases.

The relation of both initiatives is already established as many of the recruiting sites at the WP2 "Biomarkers of drug-induced liver injury" are connected or belong to the pro-euro-DILI-Network. The plan is to further continue the contact between both projects and feed each other.

5.3 i2b2 tranSMART Foundation

The i2b2 tranSMART Foundation is a member-driven non-profit foundation developing an open-source / open-data community around the i2b2, tranSMART and OpenBEL translational research platforms.

The i2b2 tranSMART Foundation enables effective collaboration for precision medicine, through the sharing, integration, standardization and analysis of heterogenous data from healthcare and research; through engagement and mobilization of a life sciences focused open-source, open-data community.

In TransBioLine, we have devised to set up a project-specific tranSMART data management platform. The platform will feed into the development of novel safety biomarkers and facilitate biomarker qualification.

tranSMART will provide easy and robust interface for the input of new clinical and molecular data. Several analytical tools from existing initiatives such as i2b2 tranSMART Foundation and the eTRIKS knowledge management platform will be made available.

The TransBioLine partner ITTM, as a spin-off from the University of Luxembourg in the context of the eTRIKS IMI project, brings in its in-depth expertise on working with the tranSMART plaform. Members of ITTM have previously been active contributors to the development of tranSMART in the context of the eTRIKS consortium.

5.4 CIOMS DILI working group

In 2017, CIOMS launched a Working Group composed of key stakeholders, including regulators, academia and industry partners, to address the present knowledge and practice gaps related to drug-induced liver injury (DILI). The group formulates pragmatic, consensus-based recommendations to address the issues described above.

The TransBioLine Consortium is embedded into this network of international research collaboration CIOMS DILI working group. This significant cross-linking will help to avoid overlaps and duplications, and substantially capitalize on synergies across major research sites of excellence. This collaboration will mainly bring consensus recommendations on DILI within TransBioLine.

5.5 IMI Project LITMUS

Testing Marker Utility in Steatohepatitis (LITMUS) funded by the IMI2, brings together clinicians and scientists from prominent academic centres across Europe with companies from the European Federation of Pharmaceutical Industries and Associations (EFPIA). Their common goals are developing, validating and qualifying better biomarkers for testing NAFLD.

LITMUS could bring expertise in the interpretation of "liquid biopsy" data with its development and validation of blood tests and imaging techniques to diagnose and manage NAFLD. LITMUS could bring expertise and efficiency to WP6 "Liquid Biopsies" with NGS data on NAFLD/NASH cases. Possible access to a biobank of human liver samples, and regular human liver cell isolations would also facilitate biomarker hypothesis-testing experiments. This collaboration needs to be further explored in the next months.

5.6 BBMRI-ERIC Consortium

BBMRI-ERIC is a European research infrastructure for biobanking. They bring together all the main players from the biobanking field – researchers, biobankers, industry, and patients – to boost biomedical research. To that end, they offer quality management services, support with ethical, legal and societal issues, and a number of online tools and software solutions. Ultimately, their goal is to make new treatments possible

Mediated by Charité, the TransBioLine consortium will have access to this extensive European biobank expertise and resources. First contacts with the BBMRI-ERIC have been formalized in relation to the transfer of former IMI SAFE-T samples, and so far, the contacts have been satisfactory issuing valuable recommendations.

5.7 eTRANSAFE

The IMI2 project eTRANSAFE (Enhancing TRANslational SAFEty Assessment through Integrative Knowledge Management) project works to improve the efficiency of translational safety assessment approaches during the medicines discovery pipeline.

The potential collaboration with TransBioLine has already been identified. For this, eTRANSAFE has appointed Dr Michael Merz, the TransBioLine former Coordinator and currently advisor of TransBioLOne, to become a member of the eTRANSAFE Scientific Advisory Board in order to ensure a smooth collaboration between both consortia. In

addition, some common partners (6 partners) will also guarantee that the relation can be efficiently established.

However, a formal discussion will be needed to ensure the identification and alignment of specific areas of interest, which may have special relevance for WP7. Some of the common areas of interest are with MLM and SIGNATOPE, which will analyze emerging biomarkers identified in TBL. These data will be used to support regulatory qualification of markers.

5.8 TransQST

TransQST (*Translational quantitative systems toxicology to improve the understanding of the safety of medicines*) is an IMI2 project, which started in January 2017.

Both TransQST and TransBioLine share common partners, which enable an easier relation between both projects.

The relation of both projects could highly benefit from the data and modelling approaches generated in both projects for the development of new and safer medicines, especially in the framework of WP7.

The plan is to further continue the contact between both projects.

5.9 C-PATH and PSTC

Critical Path Institute (C-Path) is a nonprofit, public-private partnership with the Food and Drug Administration (FDA) created under the auspices of the FDA's Critical Path Initiative program in 2005.

C-Path's aim is to accelerate the pace and reduce the costs of medical product development through the creation of new data standards, measurement standards, and methods standards that aid in the scientific evaluation of the efficacy and safety of new therapies.

These pre-competitive standards and approaches have been termed "drug development tools" (DDTs) by the FDA, which established a process for official review and confirmation of their validity for a given context of use.

C-Path orchestrates the development of DDTs through an innovative, collaborative approach to the sharing of data and expertise.

TransBioLine consortium is preparing to initiate the process of C-Path joining TransBioLine as a project beneficiary. The activities to be potentially performed by C-Path include:

1. C-Path to provide support for and facilitate the interaction of TransBioLine with health authority regulators for biomarker qualification efforts to be developed by TransBioLine. This will also include relationship with PMDA.
2. C-Path to support review of qualification-related dossier (data and documents) prior to health authority interactions including sharing specific elements of previous C-Path qualification efforts related to individual work packages.
3. TransbioLine to lead health authority interactions and qualification efforts, and coordinate C-Path activities as needed for individual work packages (document review/writing and associated meetings with health authorities).

Contacts with both C-Path chiefs and TransBioLine Project Officer are currently taking place for the formalization of this key incorporation into the consortium. Significant synergies are expected from this partnership that will benefit TransBioLine Project.

5.10 DILI -Sim Initiative

The drug-induced liver injury (DILI)-sim Initiative is a pre-competitive partnership between DILIsym Services, Inc. and multiple pharmaceutical companies to support development of the DILIsym modeling software. DILIsym is a mechanistic, mathematical model of drug-induced liver injury (DILI) in the form of computational software applied to predict whether new drug candidates will cause liver signals in patients and to enhance the understanding of mechanisms that contribute to liver safety signals already observed in the clinic. The goals of the Initiative are to improve patient safety, reduce the need for animal testing, and reduce the costs and time necessary to develop new drugs.

The DILI-sim Initiative is led by Dr. Paul B. Watkins, Director of the University of North Carolina Eshelman School of Pharmacy Institute for Drug Safety Sciences. Paul B. Watkins is engaged as Scientific Advisory Board member of TransBioLine to provide strategic guidance and direction for our research project. Thanks to this alliance, DILI-sim Initiative and the possible synergies with TransBioLine will emerge in the upcoming months.

5.11 FAIR4Health

The overall objective of FAIR4Health is to facilitate and encourage the EU health research community to FAIRify, share and reuse their datasets derived from publicly funded research initiatives.

The project objectives are: (1) to design and implement an effective outreach strategy at EU level based on trust building and shared benefit, (2) to produce a set of guidelines to inform a number of Research Data Alliance recommendations in order to set the foundations for a FAIR data certification roadmap to guarantee high quality of data, (3) to develop and validate intuitive, user-centered technological tools to enable the translation from raw (meta)data to FAIR (meta)data and support the FAIRification workflow, i.e., the FAIR4Health Platform and Agents, (4) to demonstrate the potential impact in terms of health outcomes and health research that the implementation of such FAIR data strategy will have through the development and validation of 2 pathfinder case studies.

This initiative will be carefully followed with the key goal of making the data outputs sustainable beyond the project lifetime.

7. Conclusion

In the first year of activity, TransBioLine is mapping the most relevant initiatives in the field. The potential for leveraging with other projects has been or is being currently analysed, without disrupting the fulfilment of the research objectives of the project. Currently, several synergies are under discussion with the expected outcome of engaging and initiate the actual collaboration towards common goals.

Synergies with other initiatives are clearly much successful where common members are shared, as the exchange of information becomes more fluent; for this reason, all project members can act as representative of TransBioLine when initiating conversations with other initiatives and play a key role for the project.

TransBioLine will continue the initiated contacts and will establish new collaborations by identifying potential synergies during the next years of the project.