PERMIT – PERsonalised MedicIne Trials

Gap analysis

Work Package 2 - Deliverable 2.5

Deliverable no	2.5
Deliverable Title	Gap analysis
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Responsible Partner	ECRIN
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Executive summary

The PERMIT project aims to produce recommendations on robust and reproducible methodologies for personalised medicine research. It will achieve this goal by performing a mapping of the research methodologies through a literature review, identifying and analyzing the existing gaps and then organizing a series of workshops to discuss and address these gaps, and draft recommendations. This document describes the main gaps that were identified through the scoping reviews, performed during the first year of the project. It also describes the transversal gaps and questions that were highlighted during the project's Gap Analysis Workshop. These were: sample size estimation required to achieve sufficient statistical power for the design of stratification and validation cohorts; validation workflows for stratification; definition of pre-clinical models for stratification and treatment selection; data quality and data management through the different stages of data generation, analysis and exploitation; and, regulatory requirements for algorithms and for generating and integrating omics data. The document also describes the next steps that will be taken, as work plans are defined for the project's second and final year.

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Background

The PERMIT project aims to produce recommendations and standards for personalised medicine (PM) research methodologies. Over the first year of the project, a series of scoping reviews of the scientific papers and grey literature has been carried out (WP2), to map the existing research methodologies, and identifying the gaps that exist along the PM research pipeline. The gaps identified correspond to different domains and can refer to, among others, to **methodological gaps**, i.e. lack of methodologies that can respond to the research questions; **regulatory gaps**, or lack of clear regulatory guidance on the methods that correspond to regulatory expectations; **gaps in harmonization or standardization**, where methodologies are applied inconsistently without clear guidelines for applicability or standards of reference, or where the heterogeneous taxonomy of methods leads to challenges in study reporting, analysis and comparison of studies. The gaps identified can also refer to the lack of technical means, where the resources needed to apply the preferred methodologies are scarce, or to the difficulty of developing or applying certain methodologies while preserving ethical principles. Identifying these gaps, and the subsequent questions to be addressed in the future recommendations is a key step in achieving the goals of the PERMIT project.

Approaches (Methods)

The detailed methodology that was followed for the conduction of the series of scoping reviews, led by IRFMN is detailed in the scoping review protocol[1], as well as in project deliverables 2.1 to 2.4. The preliminary identification of gaps was conducted by the WP leaders' teams, responsible for executing the individual scoping reviews on stratification and validation cohorts (WP3 – lead by PSSJD), machine learning and stratification (WP4 – lead by UNI-Lu), preclinical methods for translational development (WP5 – lead by EATRIS) and clinical trial designs (WP6 – lead by UPD) and reported in deliverables 2.1 to 2.4.

As part of the consultation phase of the scoping reviews, a Gap Analysis Workshop was organized, to present the findings of the scoping reviews, to discuss the gaps identified, and to define the key questions to be addressed in the process of drafting the recommendations (see Appendix II for workshop agenda). This workshop took place on December 1 and 2, 2020 online and was attended by representatives of all project beneficiaries as well as from three associated partners, the EMA, EUnetHTA and the CTFG (see Appendix I for the participant list).

Results

Through the analysis of the scoping reviews, the WP leaders identified the following preliminary gaps:

[1] Banzi, Rita, Gerardi, Chiara, Fratelli, Maddalena, Garcia, Paula, Teresa Torres, Josep Maria Haro Abad, … Jacques Demotes-Mainard. (2020, April 30). Methodological approaches for personalised medicine: protocol for a series of scoping reviews (Version V2_20200429). Zenodo. http://doi.org/10.5281/zenodo.3770937

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Stratification and validation cohorts (WP3)

1- Lack of uniform sample size calculation methods to ensure the quality and credibility of the clustering.

Integration of cohorts

2- Lack of harmonization tools for biological data and a lack of tools and methods to evaluate similarity between cohorts.
3- Lack of methodological recommendations to integrate data from different cohorts and a lack of standards of homogeneity between cohorts to be integrated, in the way of collecting the data.

Quality of the cohort data and its monitoring

4- Lack of information about required quality of data of cohorts to obtain a biomarker or multimodal data profiling.
5- Lack of requirements to monitor the collection of associated clinical data in biomarker studies

Machine learning and stratification (WP4)

1- Inadequacy of the study design and sample size selection;
2- Inadequacy and lack of robustness and completeness of the statistical evaluation;
3- Lack of clarity in the definition of clinical applications and primary/secondary outcomes;
4- Insufficient or inadequate study design documentation;
5- Inadequacy of the sampling/blocking design and the strategy to address batch effects and biases;
6- Inadequacy of the data pre-processing, filtering and normalization;
7- Inadequate or ineffective integration of prior biological knowledge and multi-omics analyses; and
8- Insufficient or inadequate measures to ensure model interpretability and biological plausibility.

Pre-clinical methods for translational development (WP5)

1- Lack of good experimental models – sufficiently robust that fully recapitulate disease phenotypes
2- Lack of methods reporting
3- Lack of standardised protocols
4- Lack of external and internal validation of models
5- Lack of systematic reviews and meta-analysis on pre-clinical methods
6- Insufficient reporting of negative results
7- Lack of regulation of the above issues

Clinical trial designs (WP6)

1- Gaps in the terminology used in labelling trial designs applied to personalised medicine,
2- Gaps in applying innovative trial designs to fields outside of oncology and
3- Gaps in implementing trials for evaluating personalised medicine strategy vs. non-personalised strategy

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Through the discussions in the workshop the following transversal questions and areas of interest for recommendations were highlighted:

1- Sample size definition in stratification and validation cohorts, and the implications of sample size definition for machine learning algorithms. This question is common to WP3 and WP4.
2- The validation process, comprehending the validation cohort, the validation of machine learning stratification and the validation of pre-clinical models. This question is also common to WP3, WP4 and WP5.
3- The use of 'supervised' machine learning to create predictive models enabling stratification (relevant to WP4) and driving the 'pre-clinical' selection (relevant to WP5) of treatments to be tested in subsequent trials.
4- Regulatory requirements and expectations on data quality and data management in the stratification and validation cohorts, in terms of source data verification, traceability, monitoring (relevant to WP3, 4 and 5). These data will drive the treatment decision in subsequent clinical trials, and in the technology will be integrated into personalised healthcare if it reaches market authorization.
5- Regulatory requirements and expectations by competent authorities on tools and methods applied in PM. For instance:
    a. the instruments used to generate omics data for the stratification cohorts. Should they be CE labelled as done for In-Vitro Diagnostics? If so, which authorities should be responsible? what evidence must be presented on their performance, accuracy, and reproducibility of measurements? (relevant to WP3)
    b. the machine learning stratification methods used to define the patient clusters. Should they be CE labeled as a medical device? If so, which authorities should be responsible and at what stage of the development and market authorization process? Would it be required to authorize a trial? At market access authorization request? From the HTAs to allow endorsement by public health systems? (relevant to WP4)

Furthermore, the question of having 'research-grade' methods for exploratory research on patient stratification, and having 'regulatory grade technologies' for market authorization and use in the healthcare systems, was raised.

Discussion and Conclusions

The series of scoping reviews through all stages of the PM research pipeline, and the subsequent Gap Analysis Workshop, lead to the identification of the main gaps and inconsistencies existing in PM research methodologies. Despite the significant volume of existing literature on PM, the gaps identified are significant in number and diverse in their nature and complexity. In order to ensure that the ambition of PERMIT can be achieved, efforts will be focused on key questions. The ambition of the PERMIT project is to contribute to more robust and reproducible PM research through recommendations. In the presentations of the Gap Analysis Workshop, the WP leaders made preliminary proposals of how the gaps could be addressed through diverse tools, such as check-lists, flow diagrams, classification tables, guidelines and more. The second year of the PERMIT project will focus on developing these tools. The participation of associated partners and other external experts will be essential to the drafting process,

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in order to produce recommendations that respond to the needs and expectations of all key PM stakeholders.

Next Steps

During December 2020 and January 2021 the WP leaders will consolidate the work plans for the second, and final year of the PERMIT Project. All efforts will be focused on drafting the recommendations, as well as on disseminating the findings of the first year. The drafting process will be structured through a series of workshops, with each WP organizing one main workshop and additional smaller workshops and working sessions. Furthermore, the transversal questions highlighted in the Results section of this deliverable, will be addressed by multi-disciplinary and inter-WP working groups. The conclusions of these working groups will also be integrated into the recommendations. In the final months of the project, training material to support the implementation of the recommendations will be produced.

The work plans for 2021 will be presented and discussed with the General Assembly in January 2021. Also during this meeting, external experts and initiatives that can contribute to the workshops and the drafting process will be identified.

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Appendix I - List of participants of the workshop

Day 1 – 1 December, 2020

Name	Organization
Ann Marie Janson Lang	CTFG
Alexander Grundmann	DLR
Emanuela Oldoni	EATRIS
Florence Beatrix	EATRIS
Jacques Demotes	ECRIN
Paula Garcia	ECRIN
Andrew Thomson	EMA
Lyudmil Ninov	EPF
Estefania Cordero	EPF
Oyvind Melien	EUnetHTA
Rita Banzi	IRFMN
Chiara Gerardi	IRFMN
Maddalena Fratelli	IRFMN
Inaki Imaz	ISCIII
Luis Sanchez	ISCIII
Setefilla Luengo	ISCIII
Mar Polo	ISCIII
Elena Toschi	ISS
Luisa Minghetti	ISS
Frank Hulstaert	KCE
Lorena San Miguel	KCE
Teresa Torres	PSSJD
Josep Maria Haro	PSSJD
Albert Sanchez	PSSJD
Irene Schlunder	TMF
Vibeke Samuelsen Fosse	UiB/EATRIS
Enrico Glaab	UNI-LU
Raphael Porcher	UPD
Cecila Superchi	UPD

Day 2 – 2 December, 2020

Name	Organization
Ann Marie Janson Lang	CTFG
Olga Kholmanskikh	CTFG

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Name	Organization
Alexander Grundmann	DLR
Emanuela Oldoni	EATRIS
Florence Beatrix	EATRIS
Jacques Demotes	ECRIN
Paula Garcia	ECRIN
Christine Kubiak	ECRIN
Mihaela Matei	ECRIN
Andrew Thomson	EMA
Lyudmil Ninov	EPF
Estefania Cordero	EPF
Rita Banzi	IRFMN
Chiara Gerardi	IRFMN
Maddalena Fratelli	IRFMN
Inaki Imaz	ISCIII
Luis Sanchez	ISCIII
Setefilla Luengo	ISCIII
Mar Polo	ISCIII
Elena Toschi	ISS
Frank Hulstaert	KCE
Lorena San Miguel	KCE
Teresa Torres	PSSJD
Josep Maria Haro	PSSJD
Albert Sanchez	PSSJD
Irene Schlunder	TMF
Vibeke Samuelsen Fosse	UiB/EATRIS
Emmet McCormack	UiB/EATRIS
Enrico Glaab	UNI-LU
Cecila Superchi	UPD

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Appendix II - Agenda of the workshop

PERMIT Gap Analysis Workshop

Agenda

01-02 December 2020

Online – Microsoft Teams

Introduction		
During this meeting the results of the scoping reviews will be presented and discussed, and the main questions to be addressed for the development of recommendations, during the second year of the project, will be identified. <u>Reading of the preparatory material for the workshop (4 scoping review reports) is essential to focus workshop time on discussions.</u>		
Meeting title:	Date(s)/time:	Location(s):
PERMIT Gap Analysis Workshop	01 and 02 December 2020 from 13:00 to 15:00	Microsoft Teams
Participants:		
ECRIN, EATRIS, UNILU/Elixir-Lu, IRFMN, PSSJD, UPD, DLR, ISCIII, KCE, TMF, ISS, EPF, EUnetHTA, EMA, CTFG		
Objective(s):		
• Present the outcomes of the scoping reviews • Collectively discuss the gaps and opportunities for recommendations • Identify all key questions to be addressed the following year		

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Day 1 – Tuesday December 1, 2020

Time:	Description:	Who:
13:00 – 13:05	Welcome and agenda	Jacques Demotes/ Paula Garcia (ECRIN)
13:05 – 13:20	Overview of scoping review – approach, protocol	Rita Banzi (IRFMN)
13:20 – 14:05	Task 2.2: Literature mapping on stratification and validation cohorts	Josep Maria Haro (PSSJD)
14:05 – 14:50	Task 2.5: Literature mapping of methods for randomised trials in personalised medicine	Raphaël Porcher (UPD)
14:50 – 15:00	Discussion and wrap up	Jacques Demotes (ECRIN)

Day 2 – Wednesday December 2, 2020

Time:	Description:	Who:
13:00 – 13:05	Welcome and agenda	Paula Garcia (ECRIN)
13:05 – 13:50	Task 2.3: Literature mapping of stratification methods	Enrico Glaab (UNI-LU)
13:50 – 14:35	Task 2.4: Literature mapping of methods used to assign treatment options to patient clusters ++++ Industry survey results	Emanuela Oldoni (EATRIS) / Vibeke Samuelsen (UiB)
14:35 – 14:55	General discussion – summary of main questions	Jacques Demotes (ECRIN)
14:55 – 15:00	Next steps and closure	Paula Garcia (ECRIN)

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