PERMIT – PERsonalised MedicIne Trials

Report on future research questions

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Executive summary

The PERMIT project had the ambition of mapping the methodologies and building methodological recommendations for the full personalised medicine (PM) research pipeline. Through the development of the recommendations and through every stage of the project we realized that certain aspects and questions would require further research and would be outside of the scope of the PERMIT project. These were questions and areas where the current evidence was insufficient to reach a solid conclusion, either because the evidence available in the literature was fragmented and/or because expertise was divergent. Considering that the PM research community could benefit from having these questions assembled in a single report, we have collated them and presented them in this document.

PM is a rapidly evolving field where innovative methodologies are being continuously being created and implemented. Addressing the questions in this report and maintaining a sustained investment in research in the field of PM including research on methods and regulatory research, will help to ensure that the highest quality of research is performed in this field, and that patients and citizens have access to safe and effective PM technologies.

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Background

The PERMIT project had the ambition of mapping the methodologies and building methodological recommendations for the full personalised medicine (PM) research pipeline. Undertaking the full pipeline allowed us to have an overview of all stages and their particular challenges, as well as their interactions and the transversal issues. It was a challenging endeavor due to the magnitude of the pipeline, the multidisciplinary expertise required to carry out the different stages and the diversity of methods applied.

From the first months of the project, as the mapping of methods and the analysis of gaps began, we realized that certain aspects and questions would require further research and would be outside of the scope that the PERMIT project could cover. These were questions and areas where the current evidence was insufficient to reach a solid conclusion, either because the evidence available in the literature was fragmented and/or because expertise was divergent.

As we moved into the development phase of our work, we were faced with the same issue. Certain areas or aspects of the methodologies applied would need further research efforts to fully consolidate evidence and provide answers to methodological and operational questions.

We felt that it would be of value to the PM research community to have these questions assembled in a single report. It will be essential to address these questions in the future to continue advancing the field of PM. This report presents the research questions that arose through the work of the PERMIT project. It does not intend to dictate future research priorities, but does provide a resource to funding bodies and programs, as they construct their future work plans in PM.

Approaches (Methods)

The questions presented in this report were collected throughout the entire development of the PERMIT project. No formal methodology was applied for the identification and collection of these questions, but significant efforts were invested in identifying them and centralizing them into this report.

During the first year, within WP2 a series of four scoping reviews were performed, each focusing on one stage of the PM research pipeline. The scoping reviews were followed by individual and transversal gap analysis to identify the areas where methodological recommendations would be needed. During these exercises, the first questions were identified.

Furthermore, in the second year of the project a series of working sessions and workshops were organized within WPs 3 to 6 with members of the consortium, associated partners and field experts. In these meetings the gaps were dissected and analyzed, and recommendations to address them were identified and discussed. This phase also identified new research questions. Then, as the recommendations were consolidated, shared and discussed with all stakeholders further questions arose. During the Implementation Workshop that was organized to present the recommendations to

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all stakeholders and jointly identify the best approaches for the dissemination and implementation of the recommendations in each stakeholder community, stakeholders pointed to additional opportunities for further research.

Finally, through the preparation of the publications on the recommendations a limited number of additional questions came up. To ensure that all questions were included in this report, the Steering Committee of the PERMIT Project (composed of all the WP leaders) gathered during a final project meeting for a brainstorming and verification session.

Results

The questions and topics to be explored in further research are presented below. They are not presented in order of priority.

- In terms of regulatory research, several questions have arisen, and future research could focus on:
    - The development of clearer guidelines for the assessment of preclinical models to ensure they are truly clinically relevant, predictable and reproducible.
    - How the regulation could better integrate the most novel patient-derived models.
    - In particular, pilot studies with feedback on lessons learned, leading to adjustments could be made at the interface of EMA/HMA and HTA domains. These pilots could help to determine how to improve dialogue between investigators and regulators, how to stimulate uptake of early consultations and move towards harmonization. Furthermore, this joint dialogue could help to ensure that the trials that are authorized will generate the evidence the HTAs need to perform full assessments.
    - Regulatory expectations on the clinical assessment of AI algorithms, and other technologies that have the capacity for continued learning.
- Although not unique to the PM setting, further research should focus on techniques, tools and accountability mechanisms to ensure a complete reporting of methods and results, including negative research findings. This is particularly urgent for pre-clinical research, where less stringent requirements are applied.
- Another field that is not unique to PM but is highly important, as a single PM research programme can apply several innovative methodologies is the validation of new methods. Additional funding resources should be directed to harmonizing the validation of new research methods. Lack of clear validation workflows was identified in all stages of the PM pipeline and further efforts to clarify best practices and regulatory expectations for validation would further advance the quality of PM research.
- Further research should be carried out on the harmonization of methods and the development of formal standards and best practices for the estimation of suitable sample sizes of stratification cohorts.
- Patient involvement in PM research should be further explored. Strategies and tools that allow patients to be involved in stages of PM research pipeline as co-designers should be identified and piloted.

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- The modeling of complex diseases using multiple preclinical methods needs to be further explored. Studies assessing different combinations and testing their validity in different disease areas need to be implemented.
- Further efforts should be directed to answering the following questions: Can preclinical trials for therapeutic options in personalised medicine be predictive of the treatment outcome for human patients? In personalised medicine, do relevant preclinical models exist? While keeping in mind that preclinical trial design implies that: treatment regimen of preclinical models must resemble what can be achieved in patients and the definition of success must resemble that of humans.
- Multi-stakeholder collaboration and research will be required to reach formal standards for the documentation of AI methodologies and the documentation and reporting of AI projects and modeling results. This will help to increase transparency and reproducibility.
- The interpretability of artificial intelligence (AI) and machine learning is attracting much attention, but further research needs to be carried out. First and foremost, the expectations and definition of "explainability"[1] of each stakeholder needs to be assessed, then efforts need to be implemented to respond to these needs and to find common ground among stakeholders. Also, it will be necessary to set thresholds for "explainability". Must explainability be prioritary over the efficiency of the machine learning model? What should be done when a "black box" model produces results with higher accuracy and reliability than a "white box" model?
- In particular, the level of "explainability" that is expected from AI technologies form a clinical perspective will need to be defined.
- Another open research question is to which extend common data processing and analysis tasks in PM projects can be automated through standardized software pipelines.
- The field of in-silico models also opens many possibilities for further research, for their application in PM. Harmonization of terminology in this field would be essential to ensure that there is a common understanding for in-silico models and in-silico trials. Further work on their added value in the PM research pipeline is needed.
- In the case where AI or in-silico models can provide sufficient plausible explanation for the biological pathways that can explain the patient stratification, and/or when models of this same nature can explain therapeutic mechanisms of action, several questions arise: will these models provide sufficient evidence to move forward to a clinical trial? What will be the regulatory requirements?
- The rapidly growing field of in-silico trials will also elicit more research in the PM field. Will these trials substitute preclinical models? Will they complement them? Or will they be integrated into an algorithm of preclinical assessment of mixed methods?
- More comparative trials that assess PM approaches vs non-personalised approaches need to be undertaken. These studies can provide the most relevant information for HTAs, but also for patient communities, payers and decision makers.

[1] In this context we refer to the definition provided by IBM – "Explainable artificial intelligence is a set of processes and methods that allows human users to comprehend and trust the results and output created by machine learning algorithms." - https://www.ibm.com/watson/explainable-ai

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- Currently the vast majority of PM scientific literature covers studies focusing on single biomarkers, but the tendency is shifting towards the analysis and implementation of complex signatures made up of multi-omics in combination with other multimodal data such as imaging, behavioral and lifestyle data, patient preferences and more. Comprehensive research will need to be implemented to assess the impact of this shift in the regulatory sphere, as well as in the methodological framework.
- Assessing and dissecting successful cases of PM technologies through each of the stages of the PM research pipeline could provide additional evidence for the PERMIT recommendations. Additionally, the piloting of their implementation in ongoing and future research projects could provide confirmatory evidence of their utility.
- Further research would also need to be carried out to interweave the methodological recommendations to the assessment of value of PM technologies, encompassing the full personalised approach, as proposed by the HEcoPerMed[2] project. How do we ensure that the right technologies reaches the right person, at the right dose, at the right time and for the right cost? How can HTAs ensure in practice that the full approach is assessed?
- The field of PM is rapidly evolving. The PERMIT recommendations will need to be updated in the future to account for all changes in the methodologies being applied, as well as the evolution of the regional and global regulatory framework.

Discussion and Conclusions

PM is a rapidly evolving field where innovative methodologies are being continuously being created and implemented. The regulatory framework, which often lags behind, must continue to evolve and must find mechanisms for rapid adaptation. The PERMIT project has identified a series of research questions both on the methodological and the regulatory front that remain unanswered. Addressing these questions and maintaining a sustained investment in research in the field of PM will help to ensure that the highest quality of research is performed in this field, and that patients and citizens have access to safe and effective PM technologies.

Next Steps

If PM is to continue being a priority area, research efforts need to be invested not only on PM programs that develop new technologies, but also directly on its methods and on regulatory research that will allow innovation to advance alongside patient safety. The questions raised in this report, which will be made publicly available, could be implemented into future funding calls of the European Partnership on Personalised Medicine, and in funding calls of individual funding agencies in the EU and beyond.

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[2] https://hecopermed.eu/wp-content/uploads/2022/04/HEcoPerMed_Positionspapier_2022_web.pdf

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