Optimizing clinical research for personalised medicine: recommendations for funders, regulators and policy makers

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Context

The International Consortium of Personalised Medicine (PM) (ICPerMed) provides a forum for the promotion of personalised medicine research and implementation. It is supported by a series of projects, funded by the European Commission, that allow the broadening of ICPerMed outreach and the implementation of its vision for PM, the so called ICPerMed family.

Clinical research in PM is essential to effectively validate personalized therapeutic diagnostic and screening approaches that can safely improve the individuals' diagnosis, care and prevention, thus contributing to solve public health challenges. To help ensure robustness and reproducibility of clinical PM research and to further advance clinical trials in PM, the PERMIT project, led by the European Clinical Research Infrastructure Network (ECRIN), developed recommendations for health policy makers, regulatory agencies and research funding organizations. PERMIT is a member of the ICPerMed family.

ICPerMed refers to the definition of the European Council Conclusion on Personalised Medicine for patients (2015/C 421/03). It states that "[...] it is widely understood that PM refers to a medical model using characterization of individuals' phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention."

Background

PM research has already delivered many valuable therapeutic and diagnostic solutions for rare diseases and cancer, and is continuously expanding to other disease areas, while exploring potential preventive approaches. However, PM research and implementation are complex, as they must respond to the most pressing needs of patients and citizens by providing precise solutions with a high value for people's health, while considering the sustainability of health systems. Furthermore, PM research requires the engagement of experts from diverse disciplines and sectors, most often across different institutions, countries or continents. Quality evidence must be guaranteed before health regulations and policies can be developed and implemented. Hence, the funding framework needs to consider the specific requirements that ensure successful PM research and implementation in health systems.

The conclusions of the PERMIT project provide guidance on the design and development of PM research programs, for every stage in the research pipeline. While PERMIT recommendations were developed with a focus on methodology, they also highlight the fundamental responsibilities of other stakeholders in the advancement and acceleration of PM. This documents presents a set of recommendations for policy makers, funding bodies and regulatory agencies based on the PERMIT conclusions, elaborated by ICPerMed working groups. Policy makers, research funding bodies and regulatory agencies play essential roles in the adaptation of research strategies to the specificities of PM. They are equally crucial for promoting the implementation of research results in health systems. The concerted efforts of all will lead to the most innovative, valuable and equitable PM solutions for patients and citizens.

Roles of key stakeholders

RESEARCH FUNDING BODIES

ensure that PM research projects address the most pressing questions for patients and healthcare providers and are methodologically sound, supporting the generation of impactful results that can be seamlessly integrated into policy and practice. Furthermore, it is important that funding strategies support PM projects that develop new technologies for the market, providing a return on public investment, and ensuring research is not blocked after the discovery stage.

POLICY MAKERS

have a crucial role in the translation of results generated by PM research into policies supporting use in clinical practice and for public health. For this, policy decisions and adoption of PM frameworks need to be supported by high quality evidence, generated by methodologically rigorous PM research that produces robust and reproducible results. Based on this evidence, health agencies will develop policies, norms and recommendations, for instance for prevention, care or reimbursement, that align and respond to the priorities of citizens, patients and sustainable health systems.

REGULATORY AGENCIES

guarantee patient safety without restricting innovation. This is a challenge given the rapid progress pace of PM research methods. Regulators firmly engaged with the research community are more able to continuously adapt regulatory frameworks, because they understand better the methodological landscape and anticipating innovations. Regulators with the capacity to assess innovative PM approaches in a timely manner will generate regulatory frameworks that facilitate adoption of innovation, better responding to patients needs in the timeliest and safest manner.

The PERMIT project

The PERMIT project launched in January 2020, bringing together experts, funding bodies, patient associations, medicine agencies, Health Technology Assessment (HTA) authorities and other key stakeholders to develop consensual recommendations for robust and reproducible PM research.

The present recommendations can provide regulators, policy makers and funders with guidance for promoting the methodological soundness of PM clinical research programs, while also highlighting key areas where additional efforts from these stakeholders are needed to collectively move the field of PM research forward.

Four main phases for the development of PERMIT conclusions:

Background information: A series of scoping reviews on scientific and grey literature, which mapped the currently used methods across the PM research pipeline. Gap analysis, to identify the areas where guidance would be of added value.

Development phase: Series of working sessions and workshops with all key stakeholder groups and field experts, to discuss the gaps and jointly define methodological guidelines and recommendations.

Finalization phase: Collaborative writing and formal consensus exercises to the define the final set of methodological guidelines and recommendations.

Implementation: With all stakeholder groups, joint definition of dissemination and implementation approach for the PERMIT conclusions. Development of scientific articles, communication and training material.

Representatives from the following stakeholders participated in the development of the recommendations: EMA, national competent authorities, research ethics committees, health technology assessment (HTA) agencies, patient associations, research funders, representatives of research infrastructures, and researchers from the academic and the private sectors, from multiple fields such as biostatistics, bioethics, molecular imaging, open science, oncology, artificial intelligence, machine learning, bioinformatics, clinical trial methodology and more.

Key challenges in clinical research for PM

The mapping of the existing literature and subsequent gap analysis by the PERMIT project identified gaps and challenges that hinder the quality of PM clinical research:

1	Insufficient evidence exists to define which methods should be favoured. This can arise when methodologies and models have not been rigorously validated and continue to be applied. One such case is the use of un-validated pre-clinical models being used to generate pre-clinical evidence.
2	Incoherence between the selected study design and the research question, for instance use of inadequate sample sizes for the selected stratification approach.
3	Scientific rigor in the selection of methods can be overcome by the ambition to apply innovative methodologies and new technologies.
4	The existing methods are not sufficiently robust and/or are unable to adequately address the needs of PM research, for example when pre-clinical models are unable to fully reproduce the disease.
5	Lack of clarity of the regulatory framework or the regulatory framework has not evolved at the same pace as the most innovative methods, creating significant challenge for researchers and discouraging the use and development of more ground-breaking methods. For example, if initial discovery research was not aligned with the regulatory framework, the initial research phases may need to be replicated and rectified when pursuing clinical validation.
6	Shortage of systematic reporting of research methods, and inconsistent reporting of negative findings, present a particular challenge for PM, leading to redundant negative findings and waste of research resources. Unnecessary duplication of efforts and research needs to be avoided. Only by thorough methods reporting can evidence be consolidated and appraised for the identification of the most robust methodologies.
7	Non-harmonized terminology in the field of PM leads to inconsistent references to clinical trial designs and lack of consensus on their characteristics, raising challenges for all the involved stakeholders.

Key areas to optimize clinical research for PM

The following are overarching areas where efforts by key stakeholders would generate the most impact towards improved PM research practices:

1	**Promoting and funding methodological research and validation studies:** • Ensure that new and innovative PM methods are robust and reproducible and thorough validation studies are performed; • Use the outcomes of validation studies to support the evolution of the regulatory framework.
2	**Engaging patients:** • Enable and encourage patient involvement and co-design at all stages of the PM research and innovation pipeline; • Facilitate and incentivize patient engagement, thereby ensuring that clinical research responds to the needs and priorities of patients.
3	**Promoting communication of negative findings and thorough methodology reporting:** • Encourage reporting of negative results by all players, in order to diminish researchwaste and enhance return on investment; • Stimulate detailed reporting of research methods and justification of the methodological approach, and beneficial practices to enhance transparency and improved research, such as registering study protocols beyondclinical trials. Promote Open Science approach to enable better methodological research.
4	**Sustaining dialogue among all the relevant stakeholders:** • Ensure all actors are aware of the evolution of methods in a timely manner and can anticipate, evaluate and integrate changes in the landscape; • Facilitate a common understanding of PM concepts and terminology; • From the early stages of research projects encourage a bidirectional dialogue between investigators/developers, regulators and policy makers; • Create platforms and tools for policy makers, regulatory authorities and funders to present and discuss innovative outcomes.
5	**Evolution and adoption of regulatory frameworks:** • Promote regulatory frameworks for PM that allow for innovation to strive while ensuring patient safety; • Consider the regulation perspective at all stages of PM research, including in exploratory stages, for patient safety, to optimize research efforts and to accelerate the pathway for new technologies to reach the patients.

Key recommendations for research funders, regulatory agencies and policy makers

The following recommendations to research funding bodies, regulator agencies and policy makers will foster the implementation of the PERMIT methodology, encouraging best practices for the PM research community and successful innovative PM solutions for patients, citizens and health systems:

RESEARCH FUNDING BODIES

Refer to the PERMIT guidelines in open funding calls and provide recommendations as a reference for reviewing processes;

Develop funding strategies and programs for validation studies and methodological and regulatory research;

Support the publication of negative findings and thorough methods reporting.

Provide funding for all stages of the research pipeline, ensuring continuity from bench to bedside.

POLICY MAKERS

Ensure that the scientific evidence used for policy making is generated by methodologically sound research, through the establishment of assessment frameworks based on PERMIT guidelines;

Support methodological and regulatory research for PM to generate high quality evidence for policy decisions;

Ensure that perspectives of all stakeholders, including patients, are considered for policy development.

Promote the use of research infrastructures that can help design and implement complex PM research, while ensuring quality and excellence in research.

REGULATORY AGENCIES

Perform regulatory research and promote up to date knowledge of innovations;

Support communication channels to stimulate dialogue with researchers from the early stages of research development;

Refer to the PERMIT guidelines to assess the methodological design of stages prior to the clinical trial stage, ensuring that evidence generated is reproducible and robust.

Impact and outlook

The success of PM is dependent on appropriate scientific and funding strategies for pre-clinical and clinical research and clinical trials. It is also reliant on suitable regulation and supportive policies for translation of research results and implementation in clinical practice and public health. Based on the PERMIT project conclusions, a set of recommendations for policy makers, funding bodies and regulatory agencies have been elaborated by ICPerMed for the successful development and implementation of innovative PM approaches. These recommendations have the potential to improve the quality of PM research outcomes, and support the seamless and timely translation of findings into therapeutic, diagnostics and preventive PM strategies. This is vital to deliver on the existing expectations for PM and provide patients and health systems with effective and valuable solutions.

Better quality PM research will not only translate into better tailored approaches for patients and citizens, but will contribute to more efficient and sustainable healthcare services through the optimized use of the existing resources.

Furthermore, it will address key public health challenges, and improve the return of public investment in research.

As the European Partnership for Personalised Medicine (EP PerMed) will start in 2023, it will create a central forum for interdisciplinary dialogue across all sectors involved in PM. The recommendations presented in this Brief will help shape the design of the planned joint transnational calls focusing on PM research. These recommendation will further inform the debate on supporting strategies for PM, including regulatory strategies and targeted actions, and the development of policies for PM implementation in health systems.

Links:

https://permit-eu.org/

https://www.icpermed.eu/

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