Analysis of Barriers, Guidelines and Best Practices for Implementation of Results and Data Exploitation in Personalised Medicine Research Projects

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1. Introduction and Objective

The International Consortium for Personalised Medicine (ICPerMed) is a platform to support communication and exchange on Personalised Medicine (PM) research, funding and implementation. ICPerMed aims to foster and accelerate the development and implementation of Personalised Medicine approaches into the healthcare systems.

PM is defined as a targeted approach to the prevention, diagnosis and treatment of disease based on an individual's specific profile. Despite its tangible advantages, the complex process to translate PM into the healthcare systems has delayed its uptake. It involves a wide range of stakeholders and entails tackling numerous barriers for implementation.

The present document has been developed under the *Task 4.3.* of the ICPerMed Secretariat proposal *"Accelerating the implementation of the results and data exploitation of PM research project"*. Also, this document joins together two milestones: *M.4.2. "Analysis of the barriers for the implementation of the results and data exploitation of ERA PerMed research projects"* and *M.4.3. "Guidelines and best practices for the implementation of the results and data exploitation of ERA PerMed research projects".*

In order to accelerate the implementation of results and data exploitation of PM research projects, ISCIII's representatives on behalf of ICPerMed Secretariat have examined, mapped and analysed the technical and non-technical barriers and gaps of PM research projects, as well as recommendations about how to address and minimise the barriers and overcome the problems in the development and implementation of results that brings PM approaches into health systems. Hence, the aim of this study is to gather feedback from the PM community to identify barriers and solutions in the PM research field.

As ISCIII is also the coordinator of ERA PerMed, in addition to leading this work package, synergies between the work results of ERA PerMed and ICPerMed have been used and therefore, duplication of work has been avoided.

2. Methodology

In order to achieve this goal, two different tools have been used:

- First, ISCIII has conducted a survey, to identify barriers and solutions, among the 87 coordinators of research projects funded by ERA PerMed, under the Joint Transnational Calls (JTC) 2018, 2019, 2020 and 2021. This consultation was technically implemented using Google Forms: (https://docs.google.com/forms/d/e/1FAIpQLSc2L4eKO9FQK3Yng2VI4ANAq6BJHYecFvG5OSjqzTOn5wXClA/viewform?usp=sf_link).
  The survey was launched on October 27th, 2022 via email to the coordinators of ERA PerMed funded projects. The ICPerMed Secretariat shaped eight core perspectives in the survey.
  1. PM pre-clinical and clinical research settings
  2. Patients and citizens involvement
  3. Implementation of results
  4. Ethical, legal and social aspects (ELSI)
  5. Data management
  6. Health economics
  7. Health Technology Assessment (HTA) aspects
  8. The use of European Research Infrastructures (ESFRIS)

- Second, in the last ICPerMed workshop "Preparing the Future for Personalised Medicine: EP PerMed", which took place in Pamplona (Navarra, Spain) on January 17-18, 2023, a plenary session related to the topic *"Best practice of overcoming PM implementation barrier"* was organised. This session welcomed two coordinators of projects funded by ERA PerMed. The goal of this session was to show successful examples of PM projects and the main barriers that they encountered during the implementation of their research projects and how they tried to overcome these barriers. The conclusions obtained by the coordinators as well as the contribution of experts in the audience have also been used to elaborate this document and they have been included in the following section "Feedback to the potential barriers in the PM research field". The report of the Workshop is published on the ICPerMed website.

Results of the survey were analysed and presented as proportions of particular answers in relation to the total number of responses given to a specific question. The data graphs were performed using Microsoft Excel and GraphPad Prism Software v9.

3. Results

3.1. Participation description

Thirty out of 87 coordinators of ERA PerMed research projects completed the survey, which means that the participation rate was 34%. Specifically, the participation rate was similar for all calls (Table 1). The number of the coordinators of each JTC that participated in the survey is also shown in Table 1.

ERA PerMed JTC	Nº of funded projects	Nº of participating coordinators	Participation rate per call (%)
JTC2018	25	9	36
JTC2019	22	7	32
JTC2020	18	8	44
JTC2021	22	6	27

Table 1. Number of coordinators of each JTC that participate in the survey and participation rate

The 30 coordinators who responded to the survey are from 12 different countries: 11 are from Germany, four (4) from Italy, three (3) are from Spain, two (2) from Canada, two (2) from Denmark, two (2) from Finland and one each from Austria, Greece, Sweden, France, Romania and Norway.

The country distribution of respondents of each JTC is shown in the following graph (Figure 1). Germany emerged as the country with the highest number of participations with three (3) completed surveys for the JTC2018 and JTC2019, five (5) for the JTC2020 and one complete survey for the JTC2021, respectively.

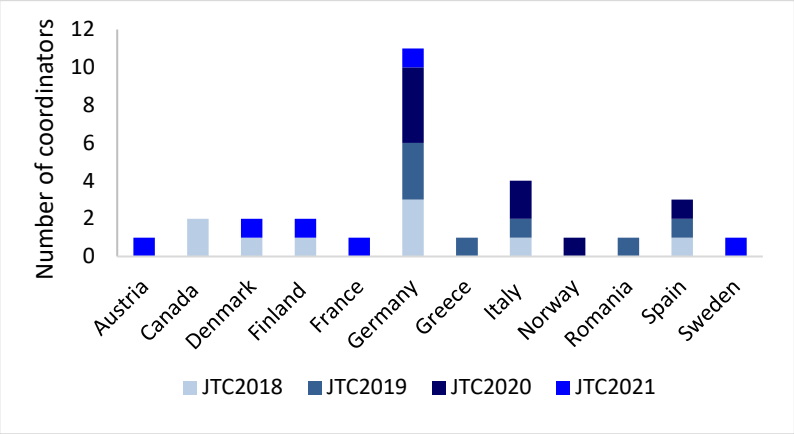

Figure 1. Country participation of respondents in each JTC (total numbers)

Regarding the gender perspective, the participation of female researchers in the survey was in total 13, which means 43,3%, calculated on the basis of 30 responders.

3.2. Feedback to the potential barriers in the PM research field

The results obtained in the questionnaire are shown below, using a Liker scale, which evaluates the degree of agreement or disagreement (with 6 response options) of the different topics during the development and implementation of research projects in the field of PM. The colour code of the legend means that the darker blue colour is, the more problematic the issue is. Thus, white colour means that coordinators do not consider this topic as a problematic in the development and implementation of the project.

Participants were asked if they encountered barriers related to the following topics, within the eight proposed categories detailed in the methodology section (Figure 2)

According to the Preclinical and Clinical Research, respondents generally considered the main barriers to be found in: 1) the regulatory framework for clinical trials; 2) patients enrolment in clinical trials; 3) clinical trials design; 4) lack of funding; 5) biomarkers identification and validation; and 6) machine-learning and big data.

Second, four key points were analysed under the topic Patients Involvement, being “Trust in data privacy” the most problematic issue.

The third topic proposed was “The Implementation of the Results”, in which participants pointed the “Translation to health system” the main barrier encountered.

In addition, based on the answers of this survey, the most significant hurdles found during the development and implementation of the PM research projects are related to ELSI aspects, such as Legal frameworks, Ethical concerns and Communication and dissemination, and mainly to Data Management topic. Participants found barriers in all categories: Data protection, Sharing data, Data storage, Data use and reuse, and Data collection.

Furthermore, the issue of Cost-Effectiveness related to Health Economics topic and the Evaluation of PM application also are some of the difficulties encountered by the coordinators of PM research projects.

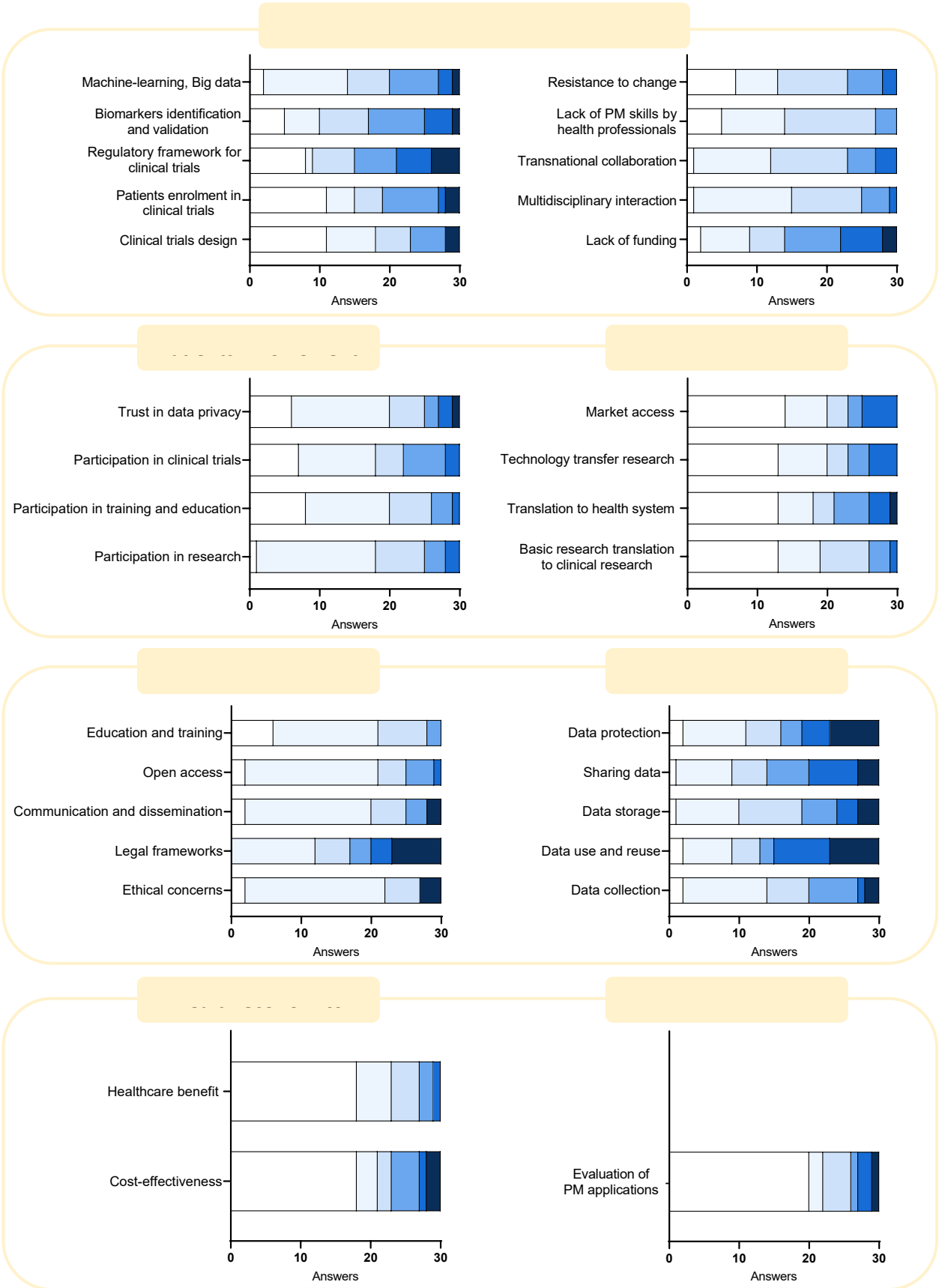

Figure 2. Summary of the degree of agreement of the main barriers in the development and implementation of PM projects by researchers, on a scale of 1 to 6 (from least to most problematic issue), represented by colour coding: white colour corresponded to "minor problem" and dark blue means "major problem". The categories analysed are: 1) pre-clinical and clinical research; 2) patients involvement; 3) implementation; 4) ethical, legal and social aspects; 5) data management; 6) health economics; and 7) health technology assessment.

Following is a detailed description of the degree of difficulties encountered by the coordinators in relation to the eight (8) proposed topics, as well as the possible solutions, recommendations and suggestions adopted or planned by the project consortium members (Table 2).

Barriers, gaps	Solutions, recommendations adopted by researchers
PRE-CLINICAL AND CLINICAL RESEARCH SETTINGS	
Resistance to change	- To get more evidence - Flexibility and adaptation of activities to financial availability
Lack of PM skills by health professionals	- Training and educate all team members - To keep qualified people as long as possible - Start new collaborations with groups with complementary skills - Increase the number of consortium members
Transnational collaboration	- Different clinical procedures can be addressed in the clinical trial protocol design - A support for PM projects with a group of experts, even involved in previous projects - Close supervision of partners who do not cooperate efficiently
Multidisciplinary interaction	- Continuous communication across disciplines - Cross fertilisation between clinical and pre-clinical researchers - Extend international collaboration - Work closely - To stablish a unique portal for all partners regardless of country to avoid redundant information and work in the administrative tasks
Machine-learning, Big data	- Tight multidisciplinary cooperation - Online tools - Integration of clinical data - Build generic integration engines that can support extraction of data - European support for biobanks and registries for existing rare disease specific networks
Biomarkers identification and validation	- Robust validation and pilot studies
Regulatory framework for clinical studies	- Participation of experts as part of the interdisciplinary team - To start ethics approval as soon as possible before project start - Explain thoroughly the study setting and the expected outcome of the study - To employ professionals who focus on law and ethical aspects
Patients enrolment in clinical studies	- Through a multidisciplinary approach, working with patients and their families. - More time for recruitment - Provide training and courses for patients
Clinical design studies	- Interdisciplinary groups - Change the eligibility criteria to enrol more patients

Lack of funding	- Applied for more funding, different national and international calls - More institutional support - Calls with longer project duration
PATIENTS AND CITIZENS INVOLVEMENT	
Patients and citizens involvement in research projects of PM	- To involve patient associations, representatives, organisations and advocates at European, national, regional and local level - To create a link between researchers and European patient's associations - To try a closer contact with patients by healthcare professionals - Education programmes for patients and citizens by government - To define clearly the aims and conditions - To explain in non-technical and plain language the project to patients - Supporting and training from communication office - Inviting patients, patient's associations, patient's advocacy organisations as well as citizens to scientific events
IMPLEMENTATION	
Market access *Technology transfer research* *Translation basic into clinical research* *Translation to healthcare system*	- Cooperation with companies - Personal motivation - Plan how to scale-up and provide best practices - Conducting pilot studies - Training and education to healthcare professionals - Research projects with longer duration
ETHICAL, LEGAL AND SOCIAL ASPECTS	
Ethical concerns in PM research projects *Legal frameworks*	- Working in synergy with the Ethics Committees to speed up bureaucratic procedures - To find ways to develop new solutions and conduct evaluation studies without having to wait 2-3 years for approval - Lawyer profiles in work teams - European ethical guidelines
Results dissemination to society	- Lay language and common terminology - Establish good communication strategies and levering the right communication tools
Education and training	- Fostering and facilitating the exchange of young researchers between international research institutions - Disseminate educational materials
DATA MANAGEMENT	
Data management	- Use existing data sets to train Artificial Intelligence (AI) models - Provide Open Data, Open Algorithms - Create simulated or algorithm data sets - Develop Information Communication Technology (ICT) tools for data management

	- Develop a systematic electronic health record with standardised terms - Use pseudonymised and anonymised data - Increase support from the national General Data Protection Regulation representatives - Multidisciplinary teams with legal support, or involvement of the legal departments of institutions - Harmonise data management regulatory policies - Start with data regulatory agreements before project start, or to have a legal research project running in parallel
HEALTH ECONOMICS	
Healthcare benefit *Cost-effectiveness*	- Develop the project and work jointly with the different structures of the health systems - More flexible approach to coverage of new methods - Showing patient benefits - Appropriate cost-effectiveness studies - More financial support - Establish a record of the cost and benefits of PM
HEALTH TECHNOLOGY ASSESSMENT ASPECTS	
Evaluation of PM applications	- Test the real implementation and viability of actual use of PM technologies in the clinical settings - Clinical standardisation of genomic sequencing, biomarkers assessments - Clinical validation of findings
EUROPEAN RESEARCH INFRASTRUCTURES (ESFRIS)	
Use of ESFRIS	- Dissemination of the use, exploitation and benefits of ESFRIS - Provide specific information to access the ESFRIS services
Use of biobanks	- To simplify to get permission to sample request and to transfer samples across borders - Resources for fostering and expanding the potential of biobanks

Table 2. Solutions adopted by researchers and their recommendation to overcome the barriers encountered during the development of the project, related to pre-clinical and clinical research; patients and citizens involvement; implementation of results; ethical, legal and social aspects; data management; health economics; health technology assessment and the use of ESFRIS.

4. Conclusions

This study aimed to identify the potential obstacles faced by researchers in the field of PM during the development of the project and its implementation in the clinical practice, as well as to show the solutions they have adopted to overcome the difficulties encountered.

Although the participation of the researchers was not as high as expected, and therefore the results obtained are not completely representative, since about 60% of the coordinators did not complete the survey, several conclusions can be drawn from the results:

The most significant barriers and challenges reported by researchers are those that fall into the category of data management, such as data protection, sharing data, data storage, data use and re-use and data collection. Similarly, ethical, legal and social aspects are also considered a major obstacle to overcome in these projects, for example the regulatory framework for clinical trials. Likewise, these topics were widely discussed at the Pamplona Workshop, thus reinforcing the results obtained in this survey. Both, the participants in the questionnaire and the researchers and experts who participated in the Workshop, highlighted the importance of multidisciplinary teams, with experts involved in legal, economic and ethical issues, due to regulatory and ethical subjects are very complex for scientists and they need a specialised support to manage these aspects.

Funding is also one of the key points in the development of PM research projects. Generally, the project takes more time than the financial life of the project, so researchers have to apply for additional funds.

In addition, participants noted that it would be desirable to provide greater visibility of the different types, access, benefits and impact of ESFRIS use in the achievement of their research projects, as they are more familiar with other national scientific resources.

The information, opinions, and those issues that have aroused most interest or controversy among the researchers have been collected and will be of great use in planning future activities within the framework of ICPerMed.

Moreover, the derived recommendations to overcome these stumbling blocks will further be considered in the European Partnership for Personalised Medicine (EP PerMed), and will aid the different stakeholders involved in the integration of PM into the healthcare. In view of these results, EP PerMed will be able to address which of these recommendations and the elimination of possible barriers are a priority, feasible in the short and medium term, or can be implemented.

In the future, the difficulties encountered by the scientific community in the field of PM could be reanalysed to assess whether the measures adopted have been beneficial and have had an impact on their implementation.

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Conflict of interest

The authors declared no competing interest for this work.

Author contributions

The development of the questionnaire was done by the Secretariat of the ICPerMed. The technical implementation of the survey was done by ISCIII members (Cristina Nieto García, Candi Sánchez Barco y María Callejo Arranz), which also performed the analysis of the survey results and wrote the manuscript.

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