PERMIT – PERsonalised MedicIne Trials

Inventory of ethical and data protection issues in personalised medicine research

Work Package 1 - Deliverable 1.3

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Executive summary

Aiming to complement the development of the methodological recommendations, an inventory of the ethical and data protection issues that can arise throughout the personalised medicine (PM) research pipeline was carried out within the PERMIT project. A dedicated workshop was organized by a multidisciplinary task force, to collect input regarding the ethical implications of personalised medicine research from the perspective of ethics experts as well as patient representatives.

Three key topic areas were addressed in the dedicated workshop, which was the basis for the inventory: patient autonomy, study co-design and access to personalised medicines technologies. In terms of patient autonomy key questions were raised regarding: the informed consent process and the time allocated to this process; the double role that healthcare professionals (HCPs) can play as physicians and researchers and its impact on the patient-HCP relationship; the importance of training all HCPs involved in research about the particular ethical and methodological challenges of PM research; the development of new tools to complement the informed consent process and the complexities of dynamic consent, as well as the new models for inclusive data governance, and its impact on patient autonomy.

When addressing access to PM technologies several issues were identified. Focus should not only be on access, it should be on access to technologies that truly respond to patient needs. Associating patients to the definition of priority areas and the design of PM research programmes is essential, as is the consultation of HTAs early in the process of designing a PM research programme. From the patient perspective, the principle of equity of access was highlighted as being key, both in terms of access to technologies and access to participation in research. The specific recourse to disinvestment if a treatment has not shown it improves quality of life or has no confirmed added value was addressed as a means to ensure that access is provided to the most valuable technologies. Tools for patient reported outcomes and measures and disease specific quality of life assessment tools developed by patient groups based on a common core can help to ensure that PM research addresses the right patient concerns.

The perimeter and the definition of co-design were addressed, as was the importance of adapting the involvement of patients, their care givers and citizens in research, to allow the experience to be truly meaningful. The importance of considering patient burden when participating in a study, and determining that burden in collaboration with patient representatives is essential in PM research. This can be achieved by involving panels of patients with different levels of expertise in research in the co-design of research programmes. Providing training opportunities to patients that will allow them to be further involved in PM research design will be key, but this can only be successful if research teams are also trained on co-design. Providing compensation and recognition for co-design efforts is also essential for success.

While this inventory is not exhaustive and does not intend to present solutions for the issues it highlights, it is meant to raise awareness on these key issues, where additional research and implementation efforts could be directed.
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I. Background

Personalised medicine (PM) is a complex and rapidly evolving field that requires multidisciplinary collaborations. Seen by many as the future of medicine and the beacon of innovation, the field elicits growing attention and resources. As more and more means are directed towards this field, there is a growing interest for harmonised practices, methodological standards and clear regulatory frameworks that can ensure that PM research upholds the highest scientific and ethical standards, bringing forward solutions for patients that are safe and effective. The PERMIT project is a Coordination and Support Action funded by the European Commission’s Horizon 2020 programme. It aims to contribute to ensuring scientific excellence, robustness, and reproducibility of personalised medicine (PM) research, by developing recommendations on PM research methods.

Aiming to complement the development of the methodological recommendations, an inventory of the ethical and data protection issues that can arise throughout the PM research pipeline was carried out within the PERMIT project. While this inventory articulates with the recommendations produced by the project, it is not exhaustive and does not intend to present solutions for the issues it highlights. Fully addressing the challenges identified and defining potential solutions would require significant resources that the PERMIT consortium was not equipped to implement. Nevertheless, this inventory is meant to raise awareness on these key issues, where additional research and implementation efforts could be directed.

I.1 – The PERMIT Project

The PERMIT project brings together all stakeholders of the PM research pipeline to ensure that the recommendations contribute to the validity and acceptability of PM research findings by all.

The beneficiaries of the PERMIT consortium include following stakeholders: research institutions, Pan-European research infrastructures, funders, HTAs, patient organisations in Europe, regulatory bodies, data protection experts. Whereas associated partners of PERMIT represent stakeholders interested in the quality of evidence generated by personalised medicine research: industry, medicine agencies, ethics committees, funders, journal editors, HTAs & European authorities.

Although there are numerous definitions for personalised medicine, the PERMIT project is part of the family of projects underpinning the International Consortium of Personalised Medicine (ICPerMed), and as such, it operates under the European Council Conclusion on personalised medicine for patients (2015/C 421/03). According to this definition, personalised medicine is “[…] a medical model using characterisation 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”. The operational definition for the PERMIT project has been further refined to “a set of comprehensive methods (methodology, statistics, validation, technology) to be applied in the different phases of the development of a personalised approach to treatment,”

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diagnosis, prognosis or risk prediction. Ideally, robust and reproducible methods should cover all the steps between the generation of the hypothesis (e.g., a given stratum of patients could better respond to a treatment), its validation and preclinical development, and up to the definition of its value in a clinical setting.

Furthermore, the project has characterised the PM research pipeline as being composed of four main stages, listed below:

1- The design, building and management of stratification and validation cohorts and the -omics / multimodal data generation and management

2- The application of machine learning and cross-validation methods for patient stratification

3- The use of preclinical methods for translational development, with a focus on the preclinical methods used to assign treatments to patient clusters

4- The evaluation of treatments in randomized clinical trials with innovative designs, and the evaluation of personalised vs. non-personalised approaches

PM research programmes can cover all four stages and can also focus on a single or a couple of stages instead.

Spanning over two years and a half, the PERMIT project aims to map existing methodologies used throughout the PM research pipeline, identify gaps and challenges, develop targeted recommendations to address them, and then disseminate and support the implementation of the recommendations across stakeholder communities. During its first year, the PERMIT project carried out a scoping review of scientific publications and grey literature (following a defined protocol) to map the existing methodologies in the different stages of the PM research pipeline, and identify existing gaps and opportunities for recommendations. Each one of the four stages of the PM research pipeline was addressed in an individual review; and a common workshop was held to assess and discuss the identified gaps and challenges with all stakeholders.

Throughout the second year of the PERMIT project, a series of working sessions and workshops took place to address the specific questions identified in the scoping reviews and gap analysis. Consortium members and external experts from different stakeholder groups were invited to these meetings to discuss and debate potential recommendations that could be developed to address the gaps and challenges that were identified.

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The outcomes of these meetings were then formally translated into a series of recommendations that span the full PM research pipeline.

The final months of the project focused on the dissemination and implementation of the recommendations. Scientific publications were prepared, as well as lay summaries for the broader patient and citizen community. Training materials tailored to different stakeholder groups has been prepared and will be made available online as well. To ensure that dissemination and implementation efforts were fully aligned with all stakeholders an Implementation Workshop was held, to consult each stakeholder group on the most appropriate way to disseminate and implement the recommendations in their communities.

I.II - An inventory on ethical and data protection issues in personalised medicine research

This report aims to identify key questions and challenges that arise through the personalised medicine research pipeline from the ethical and data protection perspectives. A dedicated workshop was organized to collect input regarding the ethical implications of personalised medicine research from the perspective of ethics experts as well as patient representatives.

By conducting this workshop and performing the inventory, we wished to ensure that the patient journey and patient perspective are considered at length, in light of the development of the methodological recommendations. Furthermore, we wished to explore the particularities of PM research. The results presented in this report may be used by several stakeholders to improve their awareness and better guide their involvement of patients across the PM research pipeline. To this end, the findings may be used by patient organisations aiming to engage patient groups in PM research, or by researchers aiming to understand the ethical considerations around involving patients in PM research to better guide their involvement of patient groups.

II. Approaches (Methods)

The task force

Members of EPF, ECRIN and TMF, all beneficiaries of the PERMIT consortium, formed a task force in early 2021 to define the approach for performing a comprehensive inventory of ethical and data protection issues in PM and to carry out a dedicated workshop towards the end of this activity. The members of the task force included staff with legal, communications and project management expertise. This task force met forthrightly online to discuss and define the general approach for the inventory, then to organize a dedicated workshop, and finally to report on it. The task force came up with the main themes in the workshop, invited speakers and built the concept and all the content of the workshop, after series of consultations with various stakeholders as described below.
The initial inventory

An initial preliminary inventory of ethical and data protection issues was carried out by the taskforce. In order to identify the main ethical questions raised by research on PM the task force conducted a simple literature review of publications from life science scientific journals, as well as existing guidelines or recommendations issued by the supervisory authorities and research organizations freely available on their websites.

To go deeper into the subject, the task force narrowed down the search to publications and recommendations based on empirical studies (e.g. those assess research participants’ perceptions of precision medicine research based on the information provided through the consent form/notice)\(^4\)

In addition to the literature review, the task force analyzed concrete cases discussed throughout the workshops that were held within the PERMIT project, with consortium members and external experts, for the preparation of its recommendations during 2020 and 2021. The findings of the preliminary inventory are presented in the section II – Results. These findings helped to define the key topic areas that would be covered in the dedicated workshop - **patient autonomy, study co-design** and **access to personalised medicines technologies**.

The preparation of the workshop

Following the preliminary inventory, the task force determined that organizing a workshop with experts in ethics, patient representatives and other stakeholders would be the best way to expand the inventory and obtain diverse perspectives.

The workshop was therefore prepared through the fortnightly calls of the taskforce, who identified the experts that would be invited and defined the agenda and content of the workshop. With the aim of making the workshop as interactive as possible, it was originally planned as a hybrid meeting, where experts could meet both in a face-to-face and an online format. But due to the sanitary regulations at the time, the workshop was finally held in an online format on 22\(^{nd}\) November, 2021.

Speakers and experts to be invited to the workshop were identified within and beyond the PERMIT consortium, by consulting the PERMIT Ethics Advisory Board, the EPF network and the networks of the PERMIT Steering Committee members.


The agenda of the workshop (Appendix II) was organized around the three key topic areas that had been defined through the preliminary inventory - patient autonomy, study co-design and access to PM technologies. The participants and speakers of the workshops were clustered into these three topics to better guide the discussion. Experts were asked to prepare guiding presentations and significant time was allocated to discussion and brainstorming.

The speakers in the patient autonomy group discussed questions regarding: How informed is consent with regard to black box artificial intelligence (AI)? What can patient literacy training and lay summaries change for patient autonomy? How is minority involvement ensured and how discrimination risks associated with intrinsic bias of AI tools avoided? Incidental findings – How to deal with them in PM research?

The speakers addressing study co-design discussed: How can patients be involved in the design and implementation of trials in personalised medicine, and act as full participants from the initial stages? How to keep patient involved until the very end of the study?

Finally, the group who addressed access to personalised medicine technologies discussed: How to ensure access to PM beyond research? How to balance the social and public health perspective vs. individual interests, considering the cost of personalised medicine?

The list of participants who attended the workshop can be found in Appendix I.

### III. Results

#### III.1 - Preliminary questions identified

Through the initial literature review and internal brainstorming of the taskforce several preliminary ethical questions were identified and divided into **3 initial categories:**

1. Challenges raised by the informed consent process
2. Increased risk of exacerbation of existing disparities in healthcare caused by disparities in the implementation of PM research results
3. Ethical challenges around the new designs and the creation of evidence

In particular, regarding the challenges raised by the informed consent process, we identified the following issues:

- Difficulty to understand/explain the design of this type of research (as compared to classical clinical trials on therapeutics or medical devices)
• High risk of therapeutic misconception: participants derive direct benefits because they will undergo testing that could lead to additional clinically relevant information
• Misunderstanding between precision treatments and standard of care
• Poor/lack of understanding of the impact of "personalised" treatment
• Difficulty to explain the risks and benefits where no reference of standard of care is available for the particular subset of patients
• Difficulty to explain the full breadth of consequences and impact of the test results (individual, family)

In terms of the increased risk of exacerbation of existing disparities in healthcare caused by disparities in the implementation of PM research results, the following issues were identified:

• Limited evidence base available to guide clinical use
• The lack of data from diverse population: treatment regimens tailored for certain patient subgroups who suffer from the same disease (what about the other groups?); exclusion of certain ethnic groups due to lack of genomic data;
• Complicated or inexistent access to modern technologies due to financial or institutional barriers;
• Incapacity of hospitals to invest in new technologies;
• Lack of appropriate financial models to implement PM in daily clinical practice

Furthermore, the following issues were identified in terms of the ethical challenges around the new designs and the creation of evidence:

• Complexity of determining when evidence has reached a sufficient level of certainty to support clinical introduction; while responding to pressure for new solutions where none or few exist;
• Challenges for regulatory authorities and ethics committees when assessing the protocols if the committees are insufficiently trained in the study designs;
• The emergence of new trial and study designs (adaptive studies, basket and umbrella designs, etc): determine criteria for ethical evaluation

In addition to the challenges listed above, the following were also identified the following concerns:

• Rapid access to innovation versus evidence-based access
• Involvement of patients in trial design: challenges specific to precision medicine
• Privacy concerns specific to PM research: protection of genetic/genomic data
• Social justice and PM

Based on these findings, the three key topic areas of the dedicated workshop were defined:

- **Patients' autonomy and PM research**
- **Access to personalised medicine technologies**
III.II – Patient autonomy

The question of patient autonomy focused on the information and consent process in the context of PM. Three introductory talks, one from the clinician’s perspective, one from the patient perspective and one from the ethicist perspective were given (see Annex 2).

The following guiding questions were used to structure the discussion on this key topic area, following the presentations:

- How to make complex information fully available to patients in adequate formats and lay terms?
- How to ensure that the patient has all the information necessary to make an informed and autonomous decision?

Through workshop participants have highlighted several challenges in relation to the patient’s information process. The time slots for presenting patient information for doctors are often too short to present all information in sufficient detail. Doctors must rely on written information sheets, and other material such as pamphlets or videos and occasionally websites or apps with additional information. Nevertheless, given the particularly complex nature of PM research programmes, limited time for informed consent can reduce uptake and comprehension, and can hinder the patient-healthcare professional relationship when either party is unsatisfied of this process.

There can be a certain conflict of interest for healthcare professionals (HCPs) who are also researchers. Patients might see the same physician twice in a day playing different roles, and this can also impact the patient-physician relationship. Patients can feel that their physician has a particular professional interest in proposing that they participate in a study. Coupled with the first issue raised, if insufficient time is given for the physician to clearly explain his double role and his interests, this can negatively impact the experience for both patient and physician.

In response to these and other challenges, the workshop participants have stressed out the importance of training of physicians on the specific ethical implications of personalised medicine research and overarching complexity of personalised medicine. For example, one of the questions to be considered is: How can doctors/HCPs make sure that patients have understood the information given? The “Reformulation” of the information received could be a way for physicians to check whether the patients have properly understood the information.

In addition to stressing the importance of providing training to physicians, the participants made recommendations in regard to the use of new technologies to collect informed consent. They have pointed out the need to invest additional means in better communication and information tools, which can particularly help with the first issue raised. They stressed the importance of asking what role digital devices can play in the
information process, and assessing if they create additional barriers or truly facilitate communication. Websites and brochures in truly lay terms were identified as essential tools. However, making use of technology to facilitate knowledge shouldn’t replace the human relationship with the physician and should not create a technological barrier for accessing the study.

The question of dynamic consent or dynamic contact was also addressed. Ensuring there are options for patients to opt out when this is proposed, and that tools are adapted to avoid exclusion (technology gap) was determined to be key. Digital health solutions bring new opportunities, however, additional barriers (especially for vulnerable groups) should be addressed and overcome, where possible was voiced out by several participants.

Another ethical issue in relation to the patients’ autonomy concerns the return of results and incidental findings. The following questions were discussed: How to communicate negative results and incidental findings of complex personalised medicine research programmes in an appropriate way? How to convey the unknowns at study start and that it is impossible to know which and what kind of incidental findings might arise and when (possibly years later)? One of the recommendations made was to present diverse scenarios of incidental findings for participant and family, and to transparently lay out the unknowns.

The importance of making information on the ongoing research available to the general population, outside of the research setting was also identified as an important recommendation. Increased public understanding of concepts that can seem “magic” (i.e. genomics, artificial intelligence, and more) which are frequent in PM research, is fundamental for further involvement of patients in future studies.

In particular, the issue of data governance was widely discussed. All studies collecting, managing and processing data must have clear and transparent data management processes and a data governance model with clear rules and patient involvement. The example of the PATH Foundation where the database and biobank are fully owned and run by patients was shared. Data review boards must also systematically involve patients in defining the data access process. Furthermore, the question of how well data is protected against misuse was raised. The possibility of having insurance cover misuse would need to be explored. While full disclosure of risks associated to breaches should be clearly explained to study participants in parallel with all the potential benefits of the use and re-use of the study data.

In this same line of thought, the importance of clarity and transparency when requesting consent for the re-use of data in “different contexts“ was also raised as an important issue. PM research often relies on the re-use of data for its initial stages and can generate clinical data that can further be re-used. Creating an interface for participants to consult and monitor the use of their data was presented as an essential tool to address this. Furthermore, it would be beneficial to promote complementary solutions to those provided for in the GDPR for the re-use of study data. For example, to facilitate secondary use of data for research purposes within a robust ethical framework; promoting a shift from consent to strong governance.

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Machine learning and artificial intelligence (AI) are an essential tool in PM research programmes, as they allow the processing of very high volumes of data for the identification of patient subgroups. The “explainability” of AI and machine learning algorithms is a key issue. Significant efforts must be made by research teams to ensure that there is full disclosure of potential for bias, of “black box” methodologies, and to convey to patients the benefits but also the limits and risks of the rapidly evolving knowledge of AI. Not doing so can lead to a sense of lost autonomy from the patient perspective, as certain concepts, are not always well understood and can lead to the perception that these technologies are not in their control. Full disclosure and clear explanations through appropriate channels and support media are essential to ensure patient autonomy.

Finally, the particular supplementary challenges of personalised prevention were raised. It can be exceptionally challenging to accurately convey the risks when these have wide degrees of uncertainty. It is hence essential for the study team to develop adequate information material in lay terms that can ensure patient autonomy in decision making around the potential risks.

III.III - Access to PM technologies

This key topic was addressed through two presentations; one from the HTA perspective and one from the patient perspective (see workshop agenda in Annex 2). Two core guiding questions were identified to structure the presentations and the discussions in this area:

- How to ensure equitable access to personalised medicine technologies in the healthcare system?
- What about access to research on personalised medicine?

A first core concern was raised by the participants: It is not simply a question of access, it is a question of having access to technologies that truly respond to patient needs and that bring an added value to the existing standard of care. Associating patients to the definition of priority areas and the design of PM research programmes is essential to address this concern, and was covered in further detail in the third session of the workshop. The importance of engaging in dialogue with HTAs as early as possible when designing and preparing PM research programmes was also raised as recommendation to address this issue, as it can help to ensure study design will provide data that allows thorough assessment on added value vs standard of care.

The HTA representatives explained that the core principles for the assessing PM technologies remain the same as for other more “classical” studies; randomized clinical trial remains the standard. In particular, for PM, there has been a higher number of technologies being authorized to enter the market based on early phase and/or single arm trials– letting technologies reach the market faster with more limited evidence. Hence, the importance of Phase IV studies increases, helping to ensure that these technologies indeed perform as intended and that their safety and efficacy profiles are optimal.
Assessment and reimbursement policy based on novel designs for rare diseases, such as N=1 trials and use of historical controls remains limited. It is therefore difficult for HTAs to generalize methodologies and experience on these particular designs. Further efforts and research will need to be done to optimize the assessment of technologies that have been evaluated in these kinds of trials.

From the patient perspective, the principle of equity of access was highlighted as being key for patients, both in terms of access to technologies and access to participation in research. All forms of lottery-based or biased access should be avoided, as well as any forms of discrimination on any basis (culture, ethnicity, religion, education, geography, economic status or other). Existing guidelines for research inclusivity⁶ should be applied and all study materials should undergo true cultural adaptation. Clear and transparent access governance needs to be implemented at all levels. Implication of representative patient groups including minorities in co-design is essential for this. This point was also further addressed in the third session of the workshop.

The specific recourse to disinvestment if a treatment has shown to not improve quality of life or no added value is confirmed was presented. This could liberate resources for other technologies and create room for more innovation. Although possible, it is currently very difficult to remove technologies off the market, in particular because resources needed for rolling re-assessment are considerable and the proper infrastructure an environment for safely removing products has not been sufficiently developed.

Although this is already a reality in some places, patient involvement in HTA assessment should be standard practice. Participants highlighted that quality of life should be included in studies as an endpoint of clinical trials whenever possible, as should patient defined priority outcomes. These allow a better understanding of each particular disease and in the case of PM, of the individual patient clusters. This deeper understanding can contribute to a much clearer case-by-case definition of the benefit-risk balance for patient community; instead of a generic approach to analysis.

Finally, tools for patient reported outcomes and measures (PROM) and quality of life assessment were discussed. Participants pointed out that generic tools have been standard for many years, but can be outdated and disease specific developed by patient groups based on a common core (to ensure comparative analysis can be performed by HTA) can be more precise. In particular, for PM, the impact of monitoring devices and mobile technologies on quality of life must now also be assessed, and specific tools to properly evaluate the outcomes of these technologies in patient quality of life may need to be developed.

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Increasing diversity in research: https://ethnichealthresearch.org.uk/increasing-diversity-in-research/
III.IV - Co-design

The third and final topic that was addressed in the dedicated workshop was co-design of PM research programmes with patients. Three guiding questions were identified to structure the presentations and discussion:

- Are there any recognised/standards methodologies dealing specifically with the involvement of patients in co-design? Any particularities for personalised medicine studies?

- Which aspects of the protocols should be assessed by patient representatives? Who should be in charge of involved and at what stage (patients, statisticians, methodologists, psychologists, physicians, etc.)?

- How can patients get full retribution for time invested in co-design (compensation, indemnities, co-authorship, presentations at conferences, training opportunities, etc.)?

Two presentations were foreseen for this session, one from the patient perspective, and one from the methodologist/statistician perspective.

The discussion on this topic began with the perimeter and the definition of co-design. Patients pointed to the importance of meaningful and adapted involvement of patients in co-design. Involvement of patients, their care givers and citizens must be adapted to allow their involvement to have meaning. Involving patients from the very beginning, keeping them informed and engaged throughout the study and then summarizing the key outcomes that concern them and the community they represent is key. The particular example of the Alzheimer Europe tools was shared. Making co-design and patient involvement in trial governance a standard practice will require further engagement of all stakeholders, including funding bodies. Patient involvement in funding selection processes and in the definition of calls for funding is already the reality in certain funding agencies, but should be expanded broadly, as should the involvement of patients in peer review of scientific publications.

The importance of considering patient burden for participating in a study was raised. Burden can greatly vary between individuals and this variability should be taken into consideration. In particular for the field of PM, where more and more studies make use of monitoring/mobile/connected devices, it is important to keep in mind that monitoring and data collection can create burden for patients. Manual entry of PROMs, keeping up with study visits, and even keeping a device charged and close to the participant can create a significant mental charge. And while this notion is gradually being given more consideration in study design and planning, it is also important to consult patient communities on burden and not to simply assume that what the investigation team might consider burdensome is automatically the case for patients. Participants reported that often patient

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8 Particular example of KCE and ZonMV agencies.
communities are willing to make significant efforts, when they are given full autonomy to chose them, and when they feel the gains outweigh the challenges.

On the topic of electronic devices for monitoring, it is important to consider that if these are to be worn at all times by study participants, they can elicit unsolicited questions and observations from peers and those in the participant’s surroundings. Significant behavioural changes as part of the participation in a study can also elicit questions and can lead to stigmatization. Taking this into consideration and providing support for any risk of stigmatization is essential. Involvement of patients in the design of mobile devices and applications is reportedly low; improving this could not only lead to better outcomes for patients, it could also potentially lead to better market success for the developers.

Regarding the protection of patient data, its analysis and its potential re-use, study results were shared on patient preference for their data being analysed by AI algorithms, as opposed to humans; stating they feel less judgment.

As in other topic areas, the importance of training was stressed. Not only should patients have opportunities to be trained in PM designs and technologies; investigators from all of the interdisciplinary fields of PM should be trained in co-design. The training should be broad and should help investigators all of the stages of PM research to fully understand how they can engage patients in co-design. In order for co-design to be successful, a safe and comfortable environment, that is as inclusive as possible, should be created for all parties involved. Training should also address this key aspect.

Co-design requires significant work and time investment. Patients, citizens and care takers involved in co-design need to be reimbursed for time spent, but should also receive formal recognition of their participation. Patient co-designers should be associated to scientific and lay terms publications. Opportunities should be sought for the co-designers to be authors, presenters and/or trainers if they so wish.

A provocative debate arose around the question of “Are patient experts too much experts?”. As patients become experts in study design there can be a potential bias in their participation, as they no longer represent the “lay” patient. It is therefore important to associate patients with different profiles in co-design and to construct a transversal patient panel. The use of existing matrices to identify specific needs and specific patients who can respond is therefore important, and can be applicable in the field of PM. Furthermore, defining a solid governance for a study ensures that no single opinion has disproportionate weight.

Today no “standard methodology” exists for patient and public involvement in studies and trials. But many existing resources to support integration of PPI to study design and management exist and can be applied to PM research programmes. Further work will need to be done to refine these tools to the specific needs of PM.
IV. Discussion and Conclusions

IV.1 – Outlooks

Throughout the workshop potential recommendations were raised as issues were highlighted and described. The successful involvement of patients in numerous initiatives of rising complexity in the past decade demonstrates that all of the issues raised can be addressed and mitigated if the proper resources and commitment are mobilized.

Training of physicians and health personnel such as research nurses on the specific ethical implications of personalised medicine research will be essential, as well as training in co-design. Dedicated training programmes could be developed. These programmes could also cover communication techniques that could help research staff to develop clear information sheets, and other tools such as websites, apps, leaflets, videos etc. that could complement patient information sheets. In particular, communication techniques that can help researchers easily explain and convey of complex topics such as AI, machine learning algorithms, data breaches and incidental findings would be essential for PM research programmes. Co-design training can help to ensure that patients and citizens are associated to PM research as early as possible, and that these long and costly endeavours are taken on to address the most pressing questions for patient communities.

Exploring outside-the-box solutions for data management, and promoting more patient-managed solutions for the management of samples and databases could be a pathway for more transparent data re-use for PM that allows patients to feel empowered and involved, while pushing innovation forward.

In particular, regarding health technology assessment, the KCE report on “Evidence gaps for drugs and medical devices at market entry in Europe and potential solutions” already presents some potential solutions. Among others:

- **Comparative effectiveness should be the norm and regulatory bodies should be more stringent and enforce surveillance for those developers who commit to perform this at post-marketing**
- **Stronger collaboration between HTAs and regulators could contribute to harmonize requirements and expectations**
- **Quality of life measures should be integrated into RCTs and systematically reported; and should not be considered as confidential when generated by companies,**
- **Further training for patient communities on comparative effectiveness and on its utility to enable advocacy as payers**
- **Further transparency for patients and clinicians to know when there is no comparative effectiveness so therapeutic decisions can be made with all elements**

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Regarding patient co-design, the importance of involving patients in the design of studies from the earliest moment possible was reiterated. This is not particular for PM; but the complexity of certain PM research programmes makes patient participation in initial stages highly valuable as they can help to ensure that these hefty endeavours are indeed being taken on the answer true patient needs, and can also help to keep the vision of the programme on track to answering key questions and keeping patient needs in mind.

Ensuring equitable access to PM technologies and to PM research will remain a priority area. Universal principles, such as non-discrimination should apply to PM research and implementation. Particular care should be taken to ensure that although the PM technologies stratify and identify smaller groups or individuals with particular biomedical signatures, these should in no way lead to any form of discrimination or stigmatization.

IV.II Conclusions

PM presents many ethical and data protection issues that are common to biomedical research. But it also presents particular challenges due to: the complexity of the methodologies and designs applied in PM research programs; the use of high volumes of complex data; the nature of the data used in PM research; the re-use of the research data and the many unknowns that can exist and that must be portrayed to participants when these programs begin. Nevertheless, it is possible to properly address these issues while giving way to innovation that can bring the solutions that patient communities are seeking.

To properly address ethical and data protection issues in the field of PM, or in any research field they must first be properly identified. Although this inventory is not exhaustive, it gathers pivotal issues in the areas of patient autonomy, study and trial co-design and regarding access to PM technologies. In order for these issues to be properly addressed awareness needs to be heightened and dedicated resources must be allocated to address them. This must be done by multidisciplinary panels of experts that include broad representation of patient communities and patient experts.

V. Next Steps

The issues identified in this inventory may continue to arise across PM research programmes if awareness is not raised on their existence, and resources are not allocated to efficiently address them. The PERMIT consortium will therefore strive to make these findings broadly available. This report will be made publicly available. The possibility of translating the findings presented in this report into a scientific publication for a broad audience and into a lay summary to be made publicly available will be explored with the workshop participants and the taskforce members. Furthermore, Deliverable 7.3 – Report of future research questions, will present all
potential future research questions identified by the PERMIT project. The questions raised and identified in the process of preparing this inventory will be reported in this deliverable.
VI. References


Appendix I – Participant list

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
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<tbody>
<tr>
<td>Ana Diaz</td>
<td>Alzheimer Europe</td>
</tr>
<tr>
<td>Céline Pouppez</td>
<td>KCE</td>
</tr>
<tr>
<td>David Perol</td>
<td>Leon Berard Hospital</td>
</tr>
<tr>
<td>Diane Gove</td>
<td>Alzheimer Europe</td>
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<tr>
<td>Eric Apondo</td>
<td>Heidelberg University</td>
</tr>
<tr>
<td>Estefania Cordero</td>
<td>EPF</td>
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<tr>
<td>Frank Hulstaert</td>
<td>KCE</td>
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<tr>
<td>Irene Schlunder</td>
<td>TMF</td>
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<tr>
<td>Jacques Demotes</td>
<td>ECRIN</td>
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<tr>
<td>Jennifer Camaradou</td>
<td>PPI expert</td>
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<tr>
<td>Kaisa Immonen</td>
<td>EPF</td>
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<tr>
<td>Lorena San Miguel</td>
<td>KCE</td>
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<tr>
<td>Luca Marelli</td>
<td>U Leuven</td>
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<tr>
<td>Lyudmil Ninov</td>
<td>EPF</td>
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<tr>
<td>Mihaela Matei</td>
<td>ECRIN</td>
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<tr>
<td>Maggy Pincemin</td>
<td>AFGS</td>
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<tr>
<td>Paula Garcia</td>
<td>ECRIN</td>
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<tr>
<td>Raphael Porcher</td>
<td>U Paris</td>
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<tr>
<td>Theodora Oikonomidi</td>
<td>U Paris</td>
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<tr>
<td>Tamas Bereczky</td>
<td>PPI expert</td>
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<tr>
<td>Valentina Stramiello</td>
<td>EPF</td>
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Appendix II - Workshop agenda

Agenda Workshop
“Brainstorming on Ethical Issues in Personalised Medicine”
22 November 2021
MICROSOFT TEAMS

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Speaker</th>
</tr>
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<tbody>
<tr>
<td>10:00</td>
<td>Setting the scene: the PERMIT and aims of the workshop</td>
<td>Paula Garcia (ECRIN) + Lyudmil Ninov (EPF)</td>
</tr>
<tr>
<td>10:15</td>
<td>Preliminary identification of ethical issues</td>
<td>Mihaela Matei (ECRIN)</td>
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<tr>
<td>10:25</td>
<td>Introduction of participants – tour de table</td>
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<td>10:45</td>
<td>Patient autonomy and PM research</td>
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<td>Clinician’s perspective (10 min)</td>
<td>Eric Apondo (NCT -Heidelberg U)</td>
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<tr>
<td></td>
<td>Patient perspective (10 min)</td>
<td>Maggy Pincemin (AFGS)</td>
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<tr>
<td></td>
<td>Ethicist perspective (10 min)</td>
<td>Luca Marelli (KU Leuven)</td>
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<td>11:15</td>
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<td>Access to personalised medicine technologies</td>
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<td>HTA Perspective (10 min)</td>
<td>Frank Hulstaert + Céline Pouppez (KCE)</td>
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<td>Patients perspective (10 min)</td>
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<td>13:20</td>
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<td>14:00</td>
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<td>14:10</td>
<td>Trial co-design</td>
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<tr>
<td>Time</td>
<td>Session</td>
<td>Speaker(s)</td>
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<td>14:30</td>
<td>Discussion</td>
<td>Raphäel Porcher + Theodora Oikonomidi (UP)</td>
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<td>15:15</td>
<td><strong>Open session: what else to consider?</strong></td>
<td>Chair – Irene Schluender (TMF)</td>
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<td>15:45</td>
<td>Summary &amp; Next Steps</td>
<td>Paula Garcia (ECRIN)</td>
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<td>16:00</td>
<td>Adjourn</td>
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