Project: **PERMIT** – **PER**sonalised **M**edic**I**ne **T**rials

Methods for clinical trials in personalised medicine

Lay Summary

1. Initial State of Play

Personalised medicine (PM) is an evolving field, which aims to treat patients by providing them a specific therapy according to their individual demographic, genomic or biological characteristics. *Patient Stratification (or Grouping*) is gathering patients into disease sub-groups, where the specific pathological processes involved are better defined, thereby allowing the tailoring of interventions. There is however, a requirement for testing treatment options targeted to the characteristics of an identified group of patients before integrating them into routine care.

The concept of PM is going to impact how pharmacological treatments (the way drugs effect patients) are discovered and developed, how patients are diagnosed and treated, and how health care systems allocate their resources to maximize patient benefits. PM may be considered an extension of traditional approaches to understanding and treating disease. Ideally, it could serve to take clinical decisions based on a patient's profile (often molecular, but the concept is broader) to minimise harmful side effects, ensure a more successful outcome, and possibly help to contain costs compared with a "trial-and-error" approach to disease treatment.

Regardless of the application, any approach to PM should undergo different phases: discovery, validation and definition of usefulness from a clinical perspective. Strong methodological approaches are needed to deal with the complexity and heterogeneity of the process, as well as the range of possible applications to stratification/grouping using multidimensional data.

The evaluation of treatments in a PM context raises a certain number of challenges, especially with the development of complex innovative designs for PM trials. Some concerns about the trial methods or the way they are conducted may also exist, while it remains of foremost importance to adequately plan and conduct those trials in order to minimise the risks to miss their objectives or present safety issues.

Personalised Medicine Research

The PERMIT project mapped the general concept of methods for PM, to set the basis for the discussion on robustness and reproducibility of PM research programmes. The final goal is the identification of standards and the development of recommendations in terms of methodology of data generation, management, analysis, preclinical development and clinical trial design to improve clinical studies in PM.
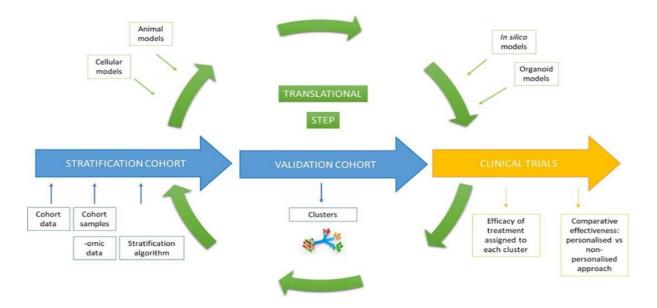
The members of the PERMIT consortium agreed on a common operational definition of **PM**

research: a set of comprehensive methods, (methodological, statistical, validation or technologies) to be applied in the different phases of the development of a personalised approach to treatment, 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 pre-clinical development, and up to the definition of its value in a clinical setting.

Scoping reviews (a form of literature review) conducted in the context of the PERMIT project explored the methods for PM research focusing on four main phases:

> - **Methods for stratification (grouping) and validation cohorts**
> - **Methods for machine learning applied to stratification**
> - **Pre-clinical methods for translational development of stratified therapies and treatments selection**
> - **Methods for clinical trials in PM**

Main steps in personalised medicine research programmes

The aim of this lay summary is to briefly present what the scoping review for clinical trials has identified and described when examining all the study designs used for clinical trials (applied to PM) and to report on the pros and cons of each.

2. Identification of the problems

Before initiating the literature review (a scoping review study), the main research questions were defined:

- ➤ What are the available designs for clinical trials applied to PM?
- ➤ What are the examples of current applications of these approaches?
- ➤ What are the pros and cons of the different approaches?
- ➤ What are the gaps in the current research on PM clinical trials?
- ➤ How is a personalised medicine strategy vs. non-personalised strategy evaluated?

3. Main Outcomes of the Scoping Review

We screened 2301 citations and 486 full-text papers; of these, 68 narrative and 6 systematic reviews were included in the final review. We identified **23 trial designs, 6 sub-types and 16 variations of trial designs** applied to PM, which we classified into four core designs: 1) Enrichment, 2) Biomarker-strategy, 3) Master protocols and 4) Randomize-all. We identified many examples of actual trials adopting the identified approaches and we extracted relevant statements on the advantages and disadvantages of each trial design. Finally, we identified 5 study designs used to evaluate a personalised vs. a non-personalised strategy.

Many innovative and complex trial designs have been proposed and implemented, especially in cancer studies, to evaluate targeted treatments in patients' groups. However, these types of trial designs raise concerns about their methodology. Strong (or robust) methodologies for clinical trials applied to PM are strongly needed to correctly select participants and treatments to be tested. Many questions on the advantages and limitations of innovative and complex trial designs are still not answered. There was also a very low number of trials comparing broadly a PM strategy to a non-personalised strategy or usual care, and a lack of guidance on when such trials are needed and how to conduct them.

The core categories are defined as follows:

Enrichment designs, where "all potentially eligible patients are first tested for the biomarker and only patients that are biomarker-positive are randomly assigned to the experimental or control treatment. Other patients are in principle excluded from further investigation in the study".

Biomarker-strategy designs allow the "inclusion of a management strategy. This strategy is not the standard or experimental treatment, but a pre-specified maker-based treatment strategy".

Master protocols refer "to a single overarching design developed to evaluate multiple hypotheses, and the general goals are improving efficiency and establishing uniformity through standardization of procedures in the development and evaluation of different interventions. Under a common infrastructure, the master protocol may be differentiated into multiple sub-

studies that run at the same time to include standardized trial operational structures, patient recruitment and selection, data collection, analysis, and management".

Randomize-all designs, where "all patients meeting the trial eligibility criteria, irrespective of their biomarker status, are randomly allocated to either experimental or control treatment".

4. Next steps & solutions

Results from the present scoping review show that **several trial designs applied to PM are available**. However, no agreement exists on the labels/ terms to use to define and classify those trials designs.

We found three main gaps related to the current research on PM clinical trials. The gaps are as follows: 1) gaps in the terminology used in labelling trial designs applied to PM, 2) gaps in applying innovative trial designs to fields outside of oncology, 3) a lack of guidance on which designs are best suited to circumvent the most important challenges in PM, and 4) gaps in implementing trials for evaluating a personalised strategy vs. non-personalised strategy.

In order to address these gaps the PERMIT project partners have worked with different actors in the PM research field and has developed a series of **18 recommendations for investigators and all interested parties** working on PM clinical trials. Seven of the recommendations are general and apply to all clinical trials in PM. Four of them are topic-specific recommendations and depend on the what the particular PM trial aims to achieve. Five of them are specific for particular designs (for basket, umbrella and platform trial designs. The last two of them are specifically on trials to assess a personalised vs a non-personalised approach.