



## **Evidence Generation Throughout the Product Life-Cycle**

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## **Contents**

Contents .....	2
1. List of Abbreviations .....	3
2. Executive summary.....	4
3. Introduction.....	5
4. Payer requirements .....	6
Background .....	6
Recommendations .....	6
5. Indirect comparisons (network meta-analysis) .....	8
Background .....	8
Recommendations .....	8
6. Single-arm studies .....	10
Background .....	10
Recommendations .....	10

## 1. List of Abbreviations

**ADAPT SMART** - Accelerated Development of Appropriate Patient Therapies: a Sustainable, Multi-stakeholder Approach from Research to Treatment-outcomes

**EMA** – European Medicines Agency

**HTA** – Health technology assessment

**MAPPs** – Medicines Adaptive Pathways to Patients

**MEAs** – Managed entry agreements

**NMA** – Network Meta-Analysis

**RCT** – Randomised controlled trial

**RWD** – real world data

**RWE** – Real world evidence

**MoCA** - Mechanism of coordinated Access on Pharmaceuticals initiative

## 2. Executive summary

ADAPT-SMART work package 1 is titled '*Evidence generation throughout the product life-cycle*' and has performed a review of IMI and non-IMI projects resulting in a gap analysis (D1.02). The gap analysis identified areas along the MAPPs pathway where tools and methods for evidence generation essential for enabling a MAPPs approach were lacking or where more tools/methods development was needed. In January 2017, a multi-stakeholder workshop reviewed and discussed the initial results of the gap analysis and reached consensus on three priority topics for which work package 1 needed to formulate more in depth research recommendations for further method, process, and/or tool development. These topics were (1) payer requirements, (2) single-arm studies, and (3) indirect comparison and observational data (network meta-analysis - NMA). Although the three are presented together in this document, the three are considered as separate and distinct pieces of work. Specifically, the (1) payer requirements was considered to be of more process / procedural and harmonisation of approaches gap, whereas (2) single-arm studies and (3) indirect comparison and observation data are seen as research-specific gaps. Other proposals which emerged as part of the second review round of outputs of IMI projects are presented in a separate gap analysis (D1.02).

Topic leads with expertise on the three priority topics were identified and draft recommendations were developed. The draft recommendations were shared with the consortium in order to elicit views on their appropriateness from all project partners. The draft recommendations were also presented to the International Advisory Board for their input and review. This document reports the final research recommendations identified in the context of work package 1. These research recommendations formulate current scientific and policy questions that require more research. The results of that research could further help different stakeholder to implement the MAPPs approach.

Payer requirement recommendations identify the need for an in-depth analysis of different pricing and reimbursement policies, how these deal with facilitating early access, uncertainty and product with immature data. Recommendations related to indirect comparisons call for the development of an NMA-plus approach that would allow for the integration of RCT and RWE in a systematic and dynamic way. Recommendations related to single-arm studies encompass the development of a framework for that establishes if and how effectiveness can be established using a single-arm studies.

### 3. Introduction

ADAPT-SMART is a multi-stakeholder consortium that was set up as a Coordination and Support Action under the EU Innovative Medicines Initiative 2 (IMI2). The ADAPT SMART consortium comprises most stakeholders in the healthcare ecosystem: patients, academics/providers, medicine developers mainly represented by the research based industry, regulators, and health technology assessment (HTA) bodies.

The MAPPs concept is a scientific concept for the development and managed access of innovative medicines and has three key components:

- a prospectively planned approach to medicine development through early multi-stakeholder dialogue involving HTA bodies;
- interactive development via approval in stages, confirming positive benefit/risk, and cycles of evidence generation and assessment;
- and the use of real world evidence (RWE) to supplement data from randomised control trials (RCT).

Work package 1 has focused on evidence generation (in a MAPPs context) throughout the product life-cycle. Earlier work has reviewed IMI and non-IMI projects that might further support different stakeholders in developing and/or implementing the MAPPs approach. This review resulted in a distinction of 'gaps' as either being horizontal along the pathway or vertical in terms of gaps in the availability, depth of or quality of the tools and methods required to support the MAPPs approach. The initial gap analysis was presented to a multi-stakeholder workshop in January 2017 to identify consensus on the gaps identified and to find consensus on the priority topics that required more detailed research recommendations. These topics were identified as being:

1. payer requirements
2. single-arm studies
3. indirect comparisons and observational data

Topic leads with expertise on these topics were found within the Consortium who developed draft research recommendations. The draft recommendations were subsequently shared with the Consortium partners for review and input. This document reports the final recommendations for further research on these topics that will enable the further development and implementation of the MAPPs approach in the European setting.

## 4. Payer requirements

### Background

The role of payers in facilitating timely access to new treatments for patients is crucial as timely access must be balanced with affordable health care systems. There is a related, but distinct role that HTA bodies and payers have in most European countries. HTA bodies will set the evidence requirements needed to inform their processes and procedures whereas payers generally base their decisions on the results of the HTA work. However, payers might have additional requirements. Until now, payers have not been actively involved in early dialogue discussions that are a key MAPPs component. This poses an issue for MAPPs to function efficiently as the need for data and evidence requirements of all stakeholders – including payers - need to be identified early on. Particularly, this might help to identify common expectations, create common data sets, registries, and other data sources, that could be used by all stakeholders. This would make the process of evidence generation – both pre and post authorisation -more efficient, transparent, predictive and less risky. Getting more and earlier clarification on payers data needs will help all stakeholders to fulfil their role along the adaptive pathway. Therefore, in order for adaptive pathways to function efficiently, the early involvement of HTA bodies and payers is essential to address the data needs they might have.

### Recommendations

- Bring learnings and achievements from current initiatives and projects together and make them available to all stakeholders such they can inform next steps on payer involvement in MAPPs. This includes the results from the IMI ‘Think Tank’ (IMiPACT) initiative and other initiatives both at EU level (e.g. SEED, EMA adaptive pathways, ADAPT SMART, MoCA) as well as globally (e.g. NEWDIGS).
- Bring together existing overviews of payers and their responsibilities in European countries, including:
  - Country/region
  - Role/responsibility
    - Advice
    - Decision maker
    - Price negotiation
    - Use of positive or negative list
    - Integral responsibility for healthcare/drug budget
    - Outpatient and/or hospital medicines
    - Separate processes for: generics, expensive drugs, orphan drugs, innovative medicines

A number of overviews exist (PPRI country reports, ISPOR website, WHO country profiles, etc) but these are not systematically updated. Therefore, a resource should be created that could maintain the country overviews. An updated

overview should be accompanied by an in-depth analysis of what systems are more or less successful in promoting (a) sustainable healthcare budgets, (b) ensuring patient access. The analysis should primarily focus on a systematic analysis of payer experiences in different healthcare systems and should combine qualitative approaches (interviews, policy documents review) with quantitative analyses (access to innovative medicines, launch delays, pharmaceutical expenditures, etc). Furthermore, specific attention should be paid to how healthcare systems deal with pricing and reimbursement of products with immature data, as this will hold valuable lessons for the implications of adaptive pathways in these healthcare systems.

- Identify the evidence requirements that the payers may have on top of the HTA process in their region. These can include:
  - Does a Minimally Important Clinical Difference (MICD) need to be defined and demonstrated?
  - What are suitable comparators to be defined?
  - Is there a requirement for demonstration of added value or is equal value enough?
  - To what degree is immature evidence acceptable?
  - Can the reimbursement level be titrated to the level of evidence and if so, how?
  - What is the capacity of the reimbursement system to handle managed entry agreements, including types like pay-for-performance, coverage with evidence development, conditional reimbursement?
  - Can the payer penalise a company for failing to deliver extra evidence in a timely manner, and if so, how?
  - Are different procedures in place for reimbursement of 'full' and 'conditional' marketing authorisations?
  - Is there a system in place for access and reimbursement for not yet licensed products (e.g. Compassionate Use, EAMS in UK)?
  - Are mechanisms in place to discontinue reimbursement of the product if new evidence shows reimbursement of the product needs to be discontinued?
- How do payers and HTA bodies in different healthcare systems deal with specific tools and methods used in drug development, such as surrogate endpoints, RWD, and extrapolation?
  - Do they accept surrogate endpoints and if so, under which circumstances?
  - Are RWD accepted and under which conditions and for which situations?
  - To which extent is extrapolation of data acceptable?

## 5. Indirect comparisons (network meta-analysis)

### Background

A key component of the MAPPs approach is the use of RWE to supplement RCT data. This will require the harnessing of large databases accompanied by a rapid turn-around of analyses in real time in order to update decisions and minimise harm. In addition, the relative effectiveness of a drug under development needs to be assessed against competitors already on the market (for HTA purposes). When few randomised studies are available to support the drug's comparative effectiveness, external information available to the drug developer might only be in the form of summary information at the aggregate patient level. Therefore, there is a challenge in how to best combine RCT data and RWD – not only from a drug developer's own data source but from published studies using aggregate information only on the effectiveness and safety of competitor drugs already on the market.

Network meta-analysis (NMA) provides a methodology for comparing RCT evidence on the safety and effectiveness of several drugs. NMA is relatively well established and has a large and growing literature. The challenge is to embed the NMA approach into a system that combines RCT data and RWD dynamically in real time to provide up to date information on a drug's performance in absolute terms and relative to that of its competitors. To further implement the MAPPs approach, methods need to be identified that will allow network meta-analysis to become embedded in a system that can integrate, in real time, moderately large RCT datasets with extremely large real world datasets and combine data at the aggregate and individual patient level. This will require the application of "Big Data" solutions to the integration of data. The data and methods used must be robust and reliable such that the outputs generated by this approach will be understandable, acceptable, and usable for decision makers (including HTA bodies and payers) and therefore, careful consideration needs to be given to the design of any interface between the data integration and the analysis on the one hand and the ease of interpretation of the resulting analyses on the other. This could be called the "NMA-plus" approach.

The development of a dynamic NMA-plus system that operates in real time would provide decision makers with a powerful tool to make comparative decisions based on the integration of RWD and RCT data. It would take advantage of not only the availability of large integrated repositories of RWD but of the increasing availability of high quality RCT data via the Data Transparency Initiative. Therefore it would be an important component of a MAPPs approach.

### Recommendations

- Review the current state of the art of traditional network meta-analysis methodology that integrates aggregate with individual patient data.



- Review the types of RWD that could be integrated into the NMA-plus approach, taking the acceptability of different decision makers into account
- Develop algorithms and software solutions that would allow the integration of RCT data and large RWD sources into the NMA-plus approach
- Test whether this approach will allow a seamless Phase II/III design integrating RCT data and RWD. The RWD would provide an enlarged placebo and active control group to feed into the NMA-plus approach. The evidence base to choose the doses to take into “Phase III” would therefore be considerably enlarged. This would allow for evidence on “effectiveness” rather than “efficacy” to be obtained while the trial(s) are running. Health Economic data could also be collected for an on-going comparative effectiveness study via the NMA-plus approach
  - An important consideration regarding this approach is whether the approach will be acceptable to regulatory agencies, HTA bodies, and payers, and for what types of products they might accept the NMA-plus approach for evidence generating rather than the ‘traditional’ drug development evidence generation
- Previous initiatives such as IMI Get Real have focussed on the integration of aggregate and individual patient data in a NMA by estimating the “usual” estimands of treatment effectiveness. An estimand can loosely be defined as “what is to be estimated”. With the publication of the draft ICH E9 addendum on estimands there will be a greater expectation on the part of the regulators for sponsors to propose more appropriate estimands. Traditional NMA will need to be modified to cope with a greater variety of estimands. This would involve the inclusion of ideas from the topic of causal inference.
- The Data Transparency Initiative will increase the availability of high-quality RCT data on competitor and/or standard of care to be used in NMA. This data will need to be integrated into the NMA-plus approach.

## 6. Single-arm studies

### Background

A key goal of MAPPs is to facilitate patients with serious diseases early access to innovative and transformative treatments. While such early access would typically be granted based on randomised evidence, in some situations it could also be granted based on non-randomised evidence alone. There have been cases of (conditional) marketing authorisations being granted based on non-randomized evidence usually generated through single-arm studies. If a product is developed using the MAPPs approach, this could include the possibility of a marketing authorisation for which the basis is a single-arm study. Therefore it is important to ensure the same evidence standard for decision making is used in these cases as for those which are based on randomised data. Single-arm studies suffer from the usual problem that separation of a study-specific effect (not treatment-related) and a treatment effect is difficult. Typically, for a single-arm study benchmarking against results from a historical (study-external) control group is used to decide whether there is a relevant treatment effect or not. Under some circumstances, however, such an approach may be impossible, e.g. if the historical control and the actual study population are remarkably different with regards to important predictors. In other situations the overlap between populations is sufficient, which may allow such a comparison versus a historical benchmark. In this situation, however, it would still be important to understand whether the strength of evidence in favour of the treatment effect is so large as to consider it sufficient for patient access in the absence of randomised evidence.

In addition, not all HTA bodies and payers accept single-arm studies as a basis for their relative effectiveness assessments. This might mean that regulatory approvals based on single-arm studies have less chance of receiving reimbursement in different countries, which is an essential step in facilitating patient access. Therefore, adequate methods need to be developed which address this problem as under MAPPs, there might be approvals based on single-arm studies.

### Recommendations

- Review the available methods and approaches that were used for approvals based on single-arm studies.
- Develop a methodological, structured framework that allows to decide whether it is appropriate to provide patient access to a novel treatment based on evidence generated by one (or multiple) single-arm studies. A key concept of this framework is to construct a (relative) treatment effect estimate from the available evidence. This will then allow benchmarking against a commonly accepted threshold, namely the one set by a (hypothetical) randomized study. If the available evidence is insufficient, the framework will allow multiple further

options, e.g. the initiation of a follow-up randomised study that incorporates the data from the preceding single-arm study

- The development of this framework will require integration of several methodological approaches, including extrapolation, causal inference, indirect comparisons and prediction. These approaches will help as follows:
  - Extrapolation may be useful to understand how the control group had performed in the actual study, had it been included;
  - Causal interference will allow for adjustment of potential confounders and correct for potential bias, therefore making patient populations more comparable;
  - Indirect comparisons will be necessary if more than one control treatment is of interest;
  - Predictions enable the use of a common and objective scale for the assessment of evidence. In particular, a predictive scale can deal with the comparisons of the generated evidence versus those from a hypothetical randomised study.
- Case studies will need to be employed to illustrate the framework.
- Assess whether the data generated this way is unbiased and reliable
- Seeking the input from regulators, HTA bodies and payers to test the usability and acceptability of the framework will be essential.
- Develop the necessary tools (guidelines, software, interactive online systems) to enable the use of the structured framework.