Discussion paper on Engagement Criteria for MAPPs

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Background on MAPPs and ADAPT SMART

Medicine Adaptive Pathways to Patients (MAPPs) is a widely-discussed concept that "*seeks to foster access to [novel] beneficial treatments for the right patient groups at the earliest appropriate time in the product life-span, in a sustainable fashion.*"[1]

MAPPs seek to address the 'evidence versus access' conundrum faced by patients, physicians, healthcare decision makers and pharmaceutical innovators. For an in-depth description of this conundrum and of the principles and goals underpinning the MAPPs approach, please refer to the following articles and website [2] [3] [4] [5].

At an operational level, MAPPs can be described as a prospectively planned approach of medicinal product development involving all stakeholders to support timely patient access to medicinal products answering a high unmet medical need.

"[MAPPs] foresee an initial marketing authorisation (MA) and reimbursement of a medicinal product in a well-defined patient subgroup and subsequent widening of the indication to a larger patient population based on additional evidence gathered and/or a conditional marketing authorisation and conditional reimbursement where initial data are confirmed [inter alia] through the collection of post-authorisation data on the medicinal product's use[6]."

MAPPs are not intended to create a new regulatory/legal framework, but instead aim to make better use of various existing tools of the current European Union (EU) procedures for medicines development and MA.

While the MAPPs concept has garnered high interest, it is clear that many aspects need to be addressed and aligned between stakeholders before it can become a reality in the EU healthcare system.

ADAPT SMART is a multi-stakeholder consortium set up as a *Coordination and Support Action* (CSA) under the EU Innovative Medicines Initiative 2 (IMI2).[7] The objective of ADAPT SMART is not to conduct primary research, but to establish an enabling platform and engage a dialogue with relevant stakeholders for the coordination of MAPPs-related activities. The consortium will conduct gap

[1] http://adaptsmart.eu/wp-content/uploads/2015/09/ProjectOverview-IMI2-ADAPTSMART.pdf
[2] Eichler et al. From adaptive licensing to adaptive pathways: delivering a flexible life span approach to bring new drugs to patients. Clin Pharmacol Ther. 2015 Mar;97(3):234-246
[3] Woodcock J. Evidence vs. access: can twenty-first-century drug regulation refine the tradeoffs? Clin Pharmacol Ther. 91:378-380 (2012)
[4] http://adaptsmart.eu/
[5] EMA reference on Adaptive pathway pilot: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp&mid=WC0b01ac05807d58ce

[6] ADAPT SMART Glossary http://adaptsmart.eu/wp-content/uploads/2016/04/D2-02-ADAPT-SMART-Glossary-first-edition.pdf
[7] http://www.imi.europa.eu/content/home

analysis to inform future research activities and engage in knowledge management activities - all with a view to facilitate and accelerate the availability of MAPPs[8].

The ADAPT SMART consortium comprises all relevant stakeholders in the healthcare system: patients, academics/providers, the research based industry, regulators, and health technology assessment bodies (HTABs). Payers are not formal partners, but some EU payer organisations are willing to engage in constructive dialogue with the consortium and have already participated in meetings and other forms of discussions.

Introduction to MAPPs Engagement criteria

An issue of divergent views became apparent early in the course of the ADAPT SMART project, namely; to what kind of novel medicines and clinical scenarios/conditions should a MAPPs approach be applied? Should MAPPs become the default pathway for most or all-new and promising products? Or should it be reserved for a small and well-defined number of exceptional medicines in development?

Other facilitated pathways[9], for example; the US FDA's 'Breakthrough Therapy Designation' or the EMA's PRIME have elaborated engagement criteria that could inform MAPPs, but these are focused on the regulatory part of the development and access. The MAPPs approach is much broader, incorporating additional stakeholders; HTABs, payers, patients and prescribers, all of whom have additional or different requirements and/or preferences. Of paramount importance is that decision-making for re-imbursement/payment is sovereign to EU Member States, which increases the complexity.

After a review of other facilitated pathways and initial discussions, it was felt that the term 'selection criteria' was too prescriptive with respects to MAPPs. For example; a product entering the MAPPs pathway does not have an official designation, it may transition out of the MAPPs pathway to the traditional pathway, and the nature of the interactions are multi-stakeholder. Therefore, the term 'engagement criteria' has been used here and hereafter with this and other ADAPT SMART documents, and will be synonymous with the term, 'selection criteria'.

Against this background, the ADAPT SMART consortium convened discussion fora with relevant stakeholders to elaborate MAPPs engagement criteria that may be broadly acceptable to all concerned within the existing legislation. In this paper, we summarize viewpoints from these discussions.

This document does not elaborate on the operational details of MAPPs, methodological considerations for knowledge generation, or actions required by different actors in the MAPPs process. The document shall not be understood or quoted as being made on behalf of, or reflecting the position of any participating organization or stakeholder, public or private. It is not intended to replace or complement official guidelines that may be in place or in development.

The paper is merely intended to inform and drive future discussions on MAPPs, both within the ADAPT SMART consortium and in the wider scientific and healthcare communities.

Engagement criteria: a set of questions

Taking account of all stakeholders' perspectives on what types of products and clinical conditions

[8] http://adaptsmart.eu/

[9] Baird et al, Accelerated Access to Innovative Medicines for Patients in Need, CPT 2014

would be eligible for MAPPs, it is important to address a set of key questions. These questions will trigger discussions initially at the company level (i.e. medicine developer) and subsequently at interaction meetings between the company and the other stakeholders. In turn, responses to stakeholders' questions will drive selection or de-selection of a product for MAPPs. The questions are listed in Figure 1 and discussed in detail below.

Figure 1: Framework of questions to be addressed by stakeholders when considering the MAPPs pathway for a given medicinal product

1. *Can we define a target population with a high unmet need? Does the product hold sufficient promise to address the unmet need?*
2. *Can a prospective iterative post- (initial) marketing authorisation development plan be proposed, developed, implemented and agreed?*
3. *Are there workable tools to ensure appropriate product utilisation?*
4. *Are there workable 'strategies' for payers in case the product under-performs?*
5. *Is there sufficient commitment and resources from relevant stakeholders to ensure successful interactions?*
6. *Which critical aspects for pharmaceutical development would need to be considered?*

1. Can we define a target population with a high unmet need? Does the product hold sufficient promise to address the unmet need?

The MAPPs focus should be on disease transformative medicines, targeting well-defined patient populations with a high unmet medical need, i.e. life threatening or severely debilitating conditions for which no treatment or no satisfactory treatment exist. Such populations will have to be identified, to the extent possible, based on objective and quantifiable medical information. Information on the disease's main features, including relevant epidemiological data, natural history, evolution with available treatment options or standard of care, and variations between countries or patients' populations will have to be addressed with reference to relevant guidelines, publications and/or registries. If relevant, the unmet medical need will be described separately for different subpopulations to select patients that could benefit best from the medicine[10].

In order to justify the benefits of early availability on the market, a MAPPs product (i.e. a product developed within the MAPPs pathway) is expected to provide clinically relevant improvements in patient-relevant outcome(s). This implies (i) a high probability that the initial promise of the product will be confirmed once more data come in and that there is a reasonable expectation of confirming added value of the product in clinical setting, and (ii) that the effect size in a considerable proportion of treated patients will be sufficient to improve the patient's daily life and/or life expectancy in a meaningful way.

A MAPPs candidate would ideally be a product for which there is a clear biological rationale, a well-understood mechanism of action and good understanding of the disease.

[10] EMA Guideline on the scientific application and the practical arrangements necessary to implement the procedure for accelerated assessment pursuant to article 14(9) of regulation (EC) No 726/2004

2. Can a prospective iterative post-(initial) MA development plan be proposed, developed, implemented and agreed?

Continuous knowledge generation throughout the lifespan of a medicine should aim to (i) achieve a rapid reduction of uncertainty around efficacy and safety in order to minimise realised patient harm, (ii) allow for broadening (or narrowing) of the treatment-eligible population where justified, and (iii) inform payers about use and effectiveness in a consistent way across Europe in order to enable flexible (adaptive) pricing schemes.

Risk Management Plans (RMPs) are currently identifying key uncertainties around safety (and efficacy) aspects and include proposed actions for reducing those uncertainties[11]. A prospective and realistic plan for conducting clinical trials and/or collecting real world evidence (RWE) post-MA would need to be discussed and agreed upon as early as possible with all relevant stakeholders. Similar to what is expected with any standard current development practice, an in-depth knowledge of the R&D environment and of the health care system(s) should be a pre-requisite to select a realistic plan.

The choice of post-MA clinical study designs would have to be based on the scientific uncertainty/question to be addressed, with specific consideration to ensuring that the selected trial will be feasible, ethically acceptable and of a design known to return reliable and interpretable results in relation to its primary objectives. In embracing the full evidence spectrum (including e.g. observational studies, pragmatic trials, or registries), stakeholders, including payers, will need to agree upfront on the type of data sources and methods of analysis most appropriate to address different questions. The design(s) should take particular account of the post-MA setting and be feasible to complete and reported upon within a reasonable timeframe.

In addition to study designs and analysis plans, the infrastructure required for data generation should be clearly and realistically defined and agreed upfront with all the stakeholders. This is to ensure (financially) sustainable pan-EU collection/analysis of post-MA data and may be based on existing disease registries, patient surveys, or access to adequate e-health records from insurance companies. Alternatively, stakeholders may agree on the creation of a *de novo* registry. An option could be a data collection system through a network of clinical 'centres of excellence' with functional capacities in terms of real-world data collection, management and sharing[12]. Setting up disease registries could be an area for early pre-competitive collaboration between stakeholders.

3. Are there workable tools to ensure appropriate product utilisation?

Unmanaged off-label use compromises sound medical practice, may harm patients, and undermines the regulators' mission of protecting patients as well as the payers' mission to make best use of limited healthcare funds. An assessment of the potential for off-label use of the product and of the opportunities to mitigate such use must be discussed at the time of MAPPs selection.

Companies which have a MAPPs product reaching the patient at an early time point - for the benefit of a specific patient (sub-) population - would need to identify a plan to limit off-label use. Such a plan could include e.g. volume of off-label threshold, educational programmes and

[11] EU GVP Module V

[12] On that point, the outcomes of the RD Platform Project (as documented here) may offer supplementary context and information.

materials for physicians and patients (i.e. guidelines and patient information leaflets), use-restrictions, etc., and would need to be agreed with all stakeholders.

Disclosure of clinical trial data, regulators' public assessment reports, and approved product information (i.e. Summary of Product Characteristics) will help providing adequate information on products' benefits and risks. In some instances, measures to ensure appropriate prescribing may be implemented by way of RMPs; these could be complemented with other tools and methods, such as drug utilisation studies and payer-initiated actions. (ADAPT SMART work package D2.7. will address this topic)

4. Are there workable 'strategies' for payers in case the product under-performs?

[*Note: 'Exit strategies' will be a topic for further discussion by the consortium. A specific work-package within ADAPT SMART is mapping this part of the process and will further explore the definitions of the notion of 'exit' from each stakeholders' perspective; the term may need to be defined or replaced by other wording once that work has matured. For the time being, 'exit strategy' is retained as a placeholder. Moreover, the working group on Managed Entry Agreement (D3.05 & D3.07 are also investigating those issues)].*

The MAPPs concept relies on continuous knowledge generation and iterative assessment of benefit-risk and value of a product. It is possible that after initial MA and reimbursement that a product in the MAPPs pathway may 'exit' MAPPs, - which could arise for a number of reasons, for example; i) MAPPs pathway ceases to add value, ii) post-MA commitments are not satisfied or, iii) product development is terminated.

There would be a need for a transparent commitment and agreement by all stakeholders up front along with a decision-making and arbitration process for determining a 'yes' or 'no' decision to continue along the MAPPs pathway and a mechanism for this and for conflict resolution to occur. Exploration of these concepts early on would reduce potential conflicts later.

5. Is there sufficient commitment and resources from relevant stakeholders to ensure successful interactions?

Multi-stakeholder interactions are of crucial importance when a MAPPs product is considered – for initial planning and to discuss appropriate corrective actions at key milestones during the product lifespan – depending on data read-outs. This could consist of the identification of key development and access steps (MAPPs moments) to align with various pre-agreed requirements and procedures; and/or to identify specific decision points (e.g. based on number of patients treated or studies completed); or what happens when the medicine gets to the prescribers and patients (e.g. are systems able to ensure only the appropriate patients get access? Are there plans to ensure prescribers are adequately trained, or advice for patients/consent and monitoring to ensure patients are safe and can give feedback?). At these moments companies, regulators, HTABs/payers will need to assess and mobilize resources to allow stakeholders to interact appropriately and a decision made, to collectively progress along the MAPPs pathway. From a practical perspective, it is understood that initially only a limited number of MAPPs products could run in parallel. Capacity to ensure appropriate/timely stakeholder interaction is not a given and will depend on each stakeholders' clear willingness and ability at many different MAPPs moments to provide the required knowledge, capacity and personnel resources to generate and analyse comprehensive datasets.

Involvement of patients in selecting product(s) entering the MAPPs pathway and in "running" the MAPPs process is key to success. Patients with specific disease experience should be partners to inform on, for example, acceptability of uncertainty levels or patient relevance of beneficial or harmful treatment outcomes. Interactions with patients' organisations (where they exist or with patient umbrella organisations) should be established as early as possible for all MAPPs products.

However, in some cases it may be difficult to gather the patients' perspectives, e.g. for some rare diseases where the patient organisation landscape is not structured; in these (exceptional) cases, the lack of patient input should not be a reason to de-select a product in the MAPPs pathway. On case by case basis, the patient inputs could be sought through the voices of patient representatives affiliated to umbrella organisations.

The present EMA's Scientific Advice framework offers opportunity to include representatives from all stakeholders concerned in the discussions via the EMA Parallel Scientific Advice.

6. ***Which critical aspects for pharmaceutical development would need to be considered?***

There should be an agreed strategy to ensure that all critical aspects of the CMC (Chemistry, Manufacturing and Controls) process provide assurance that the quality of the product will not be compromised by an early access. This should also assure the capacity to deliver consistent and reliable supplies of the MAPPs product, with controlled distribution to patients. Therefore, some modifications to the traditional CMC development paradigm are to be foreseen, as well as an intense level of dialogue between the company and the authorities concerned, in order to facilitate an effective lifespan management of the CMC documentation, and agreement on how the CMC development strategy will be implemented.

Conclusion

Discussions among the ADAPT SMART consortium members have shown that universal MAPPs engagement criteria will likely be difficult to agree upon; this reflects the reality that different actors represent sometimes opposing interests and positions in the discussions. However, consortium members representing different stakeholder groups agreed that the questions listed and explained above will be relevant and would be considered when selecting individual products for the MAPPs pathway. The answers to these questions and, ultimately, the decision to select or de-select a specific product will depend on circumstances and can only be made on a case-by-case basis. Reaching a consensus among all stakeholders depend on their willingness and ability to participate in the lifecycle of the MAPPs pathway; through appropriate and constructive discussions to allow access to transformative products to patients with high unmet medical needs.

As such this document is intended to drive further discussions and forms just part of the evolving narrative of the MAPPs pathway. It should be considered in conjunction with other ADAPT SMART documents and maybe be updated after further discussion and consultation.