



Implementing adaptive pathways - decision points and resource implications

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1. List of Abbreviations

AA – Accelerated Assessment

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

CMA – Conditional Marketing Authorisation

EMA – European Medicines Agency

HTA – Health technology assessor

MA - Marketing authorisation

MAA – Marketing authorisation application

MAPPs – Medicines Adaptive Pathways to Patients

MEAs – Managed entry agreements

PRIME – PRiority MEdicine

PRO – Patient reported outcome

PSA – Parallel Scientific Advice

RCT – Randomised controlled trial

RWD - Real world data

RWE – Real world evidence

SA – Scientific advice

EUnEHTA – European Network of HTAs

EAMS – Early access to Medicine Scheme

MoCA - Mechanism of coordinated Access on Pharmaceuticals initiative

SAG - Scientific Advisory Group (EMA)

MCDA - Multi-criteria decision analysis

EPF – European Patient’s Forum

EURORDIS - European Organisation for Rare Diseases

2. Executive summary

The introduction of a new concept introduces new dynamics to which the involved stakeholders need to adapt. When considering the feasibility and practicalities of being involved in an adaptive pathway to medicines - which includes multi-stakeholder interactions, iterative cycles of development and assessment, and long term real-world data (RWD) collection - each stakeholder must have a clear understanding of their remit (current or new), the type of input requested from them (advice or decisions), and the appropriate resources needed.

At present it is unlikely that each stakeholder will have the required capacities such as time, finance and remit, or capabilities such as specific expertise, to be an active participant in MAPPs. Therefore, the views of each stakeholder on the resources they would need to engage in MAPPs were gathered through a joint effort between D2.05 (Seamless pathway) and D3.02 (Decision points) through consensus building and workshops.

Being part of a multi-stakeholder initiative in adaptive pathways requires some specific knowledge of basic research, clinical development and regulatory requirements such as;

- Science: Disease and product-specific knowledge.
- Processes: Understanding of the MAPPs concept, regulatory tools (such as parallel scientific advice and conditional marketing authorisations), pricing and reimbursement mechanisms, cost effectiveness assessment, managed entry agreements, and prescription control tools and measures.
- Methodologies: Clinical trial design, data analysis, real world evidence generation, and small population studies.

The recommendations presented in this document should always be read in combination with the seamless pathway report (D2.05) as it builds on the key decision points identified in that document. The remits of each stakeholder remain, but new roles are emerging and the most impacted stakeholders, in terms of new resource needs and capacity to mobilize them effectively, were considered to be pricing and reimbursement authorities (including HTA), patients, and healthcare providers (HCP).

The multiple Member State-specific remits and structure for pricing and reimbursement authorities are very challenging to map in detail. They are normally not involved in early discussions, and the centralized and broad concept of MAPPs may not be applicable across all Member States. New initiatives like the joint EMA and European Network of HTAs (EuNeHTA) platform may be very important in establishing coordinated advice on development plans for early scientific advice and post-launch evidence generation.

Patient involvement is often voluntary. A mechanism to further support, educate, and expand their involvement needs to be considered, including how best to provide funding. Streamlining and prioritising involvement via a centralized broker like the European Patients' Forum (EPF) or European Organisation for Rare Diseases (EURORDIS) or umbrella organisations could help.

Healthcare professionals would need knowledge on the MAPPs concept, instructions on how to optimise real world data collection in clinical practice, and specific information on the product in question. This could be implemented via risk management plans or other tools, and co-ordinated through European Reference networks or other competent bodies.

For the adaptive pathway to become an operational multi-stakeholder tool for medicine development, we recommend to further explore 3 key components: i) The political mandate for stakeholders in member states to engage in some advising role, to enable patient-centred medicine development; ii) Leveraging existing overarching platforms to streamline resources, expertise and knowledge that will advance MAPPs capacity building for all stakeholders; and iii) Broker trust between stakeholders by exploring opportunities and methods to ensure stakeholders execute, over time, on their commitments without being bound by requests that turn out to be unreasonable or unfeasible.

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 objective of ADAPT SMART is to establish an enabling platform and engage in a dialogue with relevant stakeholders for the coordination of Medicines Adaptive Pathway for Patients (MAPPs) related activities. The ADAPT SMART consortium comprises all relevant stakeholders in the healthcare ecosystem: patients, academics/providers, medicine developers mainly represented by the research based industry, regulators, and health technology assessment bodies. Some EU payers and payer organisations are willing to engage in constructive dialogue with the consortium (although not as formal partners)¹.

The concept of MAPPs centres on 3 key facets; i) a prospectively planned approach to medicine development through early multi-stakeholder dialogue; ii) interactive development via approval in stages, confirming positive benefit: risk, and cycles of evidence generation and assessment; and iii) the use of real world evidence (RWE) to supplement data from randomised control trials (RCT). An adaptive pathway can be considered as a scientific and engagement conceptual framework through which the stakeholders collectively provide input on the best path forward for medicine development and post-authorisation access, for a particular medicine through coordinated dialogue.

¹ <http://adaptsmart.eu/>

To this end, the adaptive pathway represents an evolution away from the typical process of sequential separate stakeholder interactions and decisions. The five stakeholder categories described herein are the same as those described in the Seamless pathway. The five categories of stakeholders identified in the Seamless Pathway are: Patients; Health care professionals; Price and Reimbursement authorities; Regulators and Medicine developers. The use of categories helped describe a general MAPPs process but has some limitations. In particular, not all Member States (MS) have separate HTA capabilities or assessors to inform payers' decisions and throughout this report, HTA bodies and payers will be collectively referred to as "pricing and reimbursement authorities". "Patients" will customarily not be individual patients *per se*. In most instances, it is anticipated that a patient organization will represent patients' collective views. However, where no formal patient organization exists, patients and/or their caregivers may offer key insights through an adaptive pathway engagement process. Healthcare professionals (HCP) primarily refer to therapeutic experts involved in clinical trials or treating physicians; yet other types of expertise were regrouped in this category such as ethicists, health economists, epidemiologists, and statisticians. Therefore, a stakeholder as identified in this work does not necessarily represent a single institution, but generic insights, expertise and skills used by experts when making a certain type of recommendation or decision.

Under the current medicine development and commercialisation pathway, stakeholder remits and resources have been gradually adjusted in order to fit the requirements and permit their involvement in the key decisions during the lifecycle of medicines. However, as resources are deployed independently by each stakeholder, there is no collective understanding of the resources ultimately required for patients to get access to innovative treatment. Under adaptive pathways, multi-stakeholder engagement will require specific resource capacity and capability that might not be available today, and a better collective appreciation of the resources deployed by stakeholders.

For each stakeholder to fully immerse into a dialogue, the process must be sustainable, and offer clear benefits, and the end product must result in substantial added patient benefit. Therefore, it is an important component of developing and implementing a conceptual adaptive pathway that the different stakeholder resource requirements, and the ability to mobilize them at key decision points, are acknowledged, understood, and accounted for.

4. Working Method

As the ADAPT SMART deliverables of the D3.02 (**Decision points**) and D2.05 (**Seamless Pathway**) working groups evolved, key synergies were recognised. The remit of D2.05 was to map, within the current EU development/access pathways, the different transition/engagement moments with stakeholders, and to delineate the key process (decision) steps across the seamless pathway. In parallel, the D3.02 working group was tasked with “contrast(ing) decision points in current vs. future processes by stakeholder groups and (identifying) implications for a roadmap for implementation.” Therefore, in the initial phase of work, the D3.02 working group collaborated with D2.05 to delineate the key process steps and decision points in the seamless pathway.

Once a preliminary framework had been agreed upon, initial discussions and consensus building under D3.02 highlighted a number of practical (capacity and capability) enablers and barriers to engagement in the conceptual MAPPs pathway that could affect one or more stakeholders. On 6th July 2016, the conceptual pathway was presented during a multi-stakeholder workshop in London, UK. Concurrently, the identified enablers and barriers were explored further during 3 parallel breakout sessions at the workshop for each of the pre-defined MAPPs moments. Briefly, these consisted of:

- i) Assessment moments that are stakeholder-specific (remits are maintained as of today): Development assessment, Authorisation, Appraisal and Pricing considerations, Regulatory post authorisation decisions, and Pricing and reimbursement reassessments,
- ii) Multi-stakeholder engagement moments that may differ from today ; Agree on Adaptive Pathways as approach, Planning iterative development (covering pre and post authorisation phases), and Patient use (see Appendix A for full diagram and description of MAPPs moments).

D3.02 was tasked with mapping the shift in resources needed by each stakeholder to effectively engage in MAPPs. Based on the conceptual nature of the seamless pathway, it is premature to effectively quantify in detail the different resources needed at each decision point at this point in time. Instead, we present a consolidated summary of views expressed by different stakeholders on resources they would likely need to engage effectively in the seamless pathway.

From these summaries we derived:

1. Some general themes and questions for stakeholders to consider in their reflection on an adaptive pathway concept and their ability to engage with it.

2. Most stakeholders expressed their views in terms of practical enablers and barriers to engage in the seamless pathway. We identified which were common to all and which were stakeholder-specific, and subsequently what resources would be required in order to sustain an effective engagement in MAPPs.
3. We also explored if similar resources already existed and could be adapted to MAPPs, or if a new resource or process would be needed to support engagement with MAPPs.
4. Finally, this work led to a series of recommendations for future work towards implementing MAPPs.

Consensus building was complemented with a non-systematic review of the published and grey literature that included current multi-stakeholder initiatives, multi-stakeholder resource requirements and adaptive pathways/licensing-related literature.

For stakeholders that have a well-defined remit in the “traditional” process (i.e. as it is today) as assessors and gatekeepers, an adaptive pathway does not impact their primary responsibilities as decision makers. However, the multi-stakeholder engagement moments around the iterative development plan introduce, for some stakeholders, new roles as development advisors. This is especially the case for patient organisations and pricing and reimbursement authorities - even if most are already familiar with these roles through pilots (e.g. joint or parallel EMA - HTA scientific advice), those roles are still new to most organisations. (See also the Report on Seamless Process and Decision Points of an Adaptive Pathway). The resources identified here are based on a MAPPs concept that, at present, is generalized across Member States. As a result, this report identifies general stakeholder resources, based upon the same generalized concept. These deliberations will need to continue with all stakeholders as adaptive pathways evolve further. There are also several additional ADAPT SMART working groups with distinct objectives and deliverables with relevance to D3.02 objectives and vice versa.

4.1 Background

Current multi-stakeholder engagement initiatives between regulator, medicine developers and P&R authorities

Some of the tools and initiatives that currently encourage multi-stakeholder dialogue(s) include: i) Scientific Advice and Protocol Assistance at the EMA, ii) Parallel Scientific Advice between EMA and pricing and reimbursement authorities -

to discuss, pre-plan and maximise efficient, good quality and appropriate data collection that meets the needs of all stakeholders across the medicines lifecycle.

These initiatives centre on well-structured dialogues between stakeholders that have made great efforts to be resourced in regard to: points of contact, pre-meeting with the medicine developer, common format for dossier submission by medicine developers, a face-to-face meeting, and post-meeting minutes.

One of the learnings and recommendations that came from EMA and EUnetHTA's parallel scientific advice pilots was to maximize efficient resource utilisation, to avoid duplication of effort between stakeholders. In response, timetables and dossier submissions have since been aligned. The process has been optimised further with pricing and reimbursement authorities, providing a list of issues (to the submission dossier) and written answers ².

Other current multi-stakeholder initiatives include: the Mechanism of Coordinated Access on Pharmaceuticals initiative (MoCA) (published in 2013)³ which allowed a facilitatory voluntary mechanism for “early dialogue” between companies and competent authorities, with pricing and reimbursement authorities, patients, and other scientific experts. Confidentiality agreements were used - advice and continued involvement were non-binding. The lessons learned from the MoCA experience highlighted the need for the involved stakeholders to have an in depth knowledge of the regulatory and drug development process, and the ability to be flexible, constructive and open minded in engagement.

Additionally, EMAs Adaptive Pathways pilots (completed in 2016) ⁴ highlighted some of the resource considerations of such multi-stakeholder interactions and early dialogues under safe harbour discussions. While the safe harbour discussions were a key draw for committed and open stakeholder discussions (as preferred to legally binding), finding appropriate patient representative experience in short time frames was challenging. Pricing and reimbursement authorities' involvement was also deemed to be resource-intensive, due to the volume of simultaneous applications received, parallel participation of regulatory-pricing and reimbursement authorities in scientific advice, and the flexible and iterative nature of the discussions.

² Report of the pilot on parallel regulatory-health technology assessment scientific advice:
http://www.ema.europa.eu/docs/en_GB/document_library/Report/2016/03/WC500203945.pdf

³ Final report on MoCa:
<http://download.eurordis.org.s3.amazonaws.com/moca/history/WG%20MoCA-OMP%20Final%20Report.pdf>

⁴ Final report on adaptive pilot:
http://www.ema.europa.eu/docs/en_GB/document_library/Report/2016/08/WC500211526.pdf

5. Results

Several practical enablers and barriers to MAPPs engagement have been highlighted below. Both capacity and capability factors were identified, with the former being the main resource needs that we focus on here. These enablers and barriers should be understood as gaps that need to be addressed and would likely stimulate resource mobilisation for one or more stakeholders. In this section, we also distinguish between needs that were raised by all categories of stakeholders and between specific needs raised by one category of stakeholder. In **Figure 1** the different MAPPs assessment moments and multi-stakeholder engagement moments are depicted as per the Seamless Pathway which is set against the identified common and stakeholder specific resource needs. Further moments in the medicine lifecycle where a decision on resources might be needed are also highlighted in the picture. For example, once all stakeholders have agreed on an AP approach, additional resources would need to be planned over multiple years (i.e. estimated lifecycle of the product). The focus of our discussion is however on the major themes and stakeholder specific resources as described above.

5.1. Questions raised by all categories of stakeholders

5.1.1. Definition and prioritization of unmet need

At the time of notification that a MAPPs approach is the optimal solution for a candidate product, stakeholders should agree on the unmet need that the product aims to satisfy, as set out by the MAPPs Engagement Criteria (see Appendix B for full criteria).

Unmet need is thus contextually defined as follows⁵:

“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.**”**

Different stakeholders might still interpret differently what constitutes an ‘unmet need’.

⁵ from current Glossary of terms, and Engagement Criteria documents

Pilots in a very different context like the one conducted by the Belgian Healthcare Knowledge Center (KCE) to define unmet medical needs could provide useful learning on methods to reach a consensus⁶.

It was felt that a method documenting how a consensus was reached when considering the MAPPs engagement criteria in the context of a specific development program would be useful. The objective is for all stakeholder to harmonize their interpretation of the criteria in a specific context not unlike what is done with rating scales used in clinical trials.

5.1.2. Data sources for evidence generation

For each product utilizing a MAPPs approach, there will be a need for early identification of the infrastructures already available for further data collection of real world evidence that can be used or adapted to the development requirements. These infrastructures and the data collected should ideally be accessible to all stakeholders involved in early multi-stakeholder dialogues. Having at least greater transparency between all stakeholders as to the data collected, methods used and interpretation of the findings, compared to today, would be of great benefit.

Multiple initiatives exist to optimize registry repositories and to strengthen the value of real world data. The learnings derived from initiatives like IMI Get Real⁷, ENCePP⁸ and other projects⁹ should be used in MAPPs to support an adequate use of RWE.

5.1.3. Agreement on goals and expectations

The need to establish trust amongst all stakeholders, and in the MAPPs process itself, was the advice most often received. If each stakeholder's goals and expectations are clarified prospectively, the MAPPs process will more likely be viewed as fit for purpose and actually deliver the expected benefits. Trust builds when, "members of a network acknowledge the legitimacy of each other's goals even if they differ from one's own." ¹⁰ Stakeholders also need confidence that, upon entry into MAPPs, they can collectively agree on 'common ground'. The need to acknowledge a shared mutual goal in the form of patient centricity is key, and will enhance trust amongst stakeholders. With this enabler, there is increased confidence that commitments by all parties will be met at each decision point.

⁶ https://kce.fgov.be/publication/report/multi-criteria-decision-analysis-for-the-appraisal-of-medical-needs-a-pilot-study#.Wa_JnG996M8

⁷ <https://www.imi-getreal.eu/>

⁸ <http://www.encepp.eu/>

⁹ <https://rarediseases.org/registries-for-rare-diseases-involve-the-patient/>

¹⁰ Manring S 2007 Creating and managing inter-organisational learning networks to achieve sustainable ecosystem management, Organization & Environment, Vol. 20 No. 3, September 2007 325-346

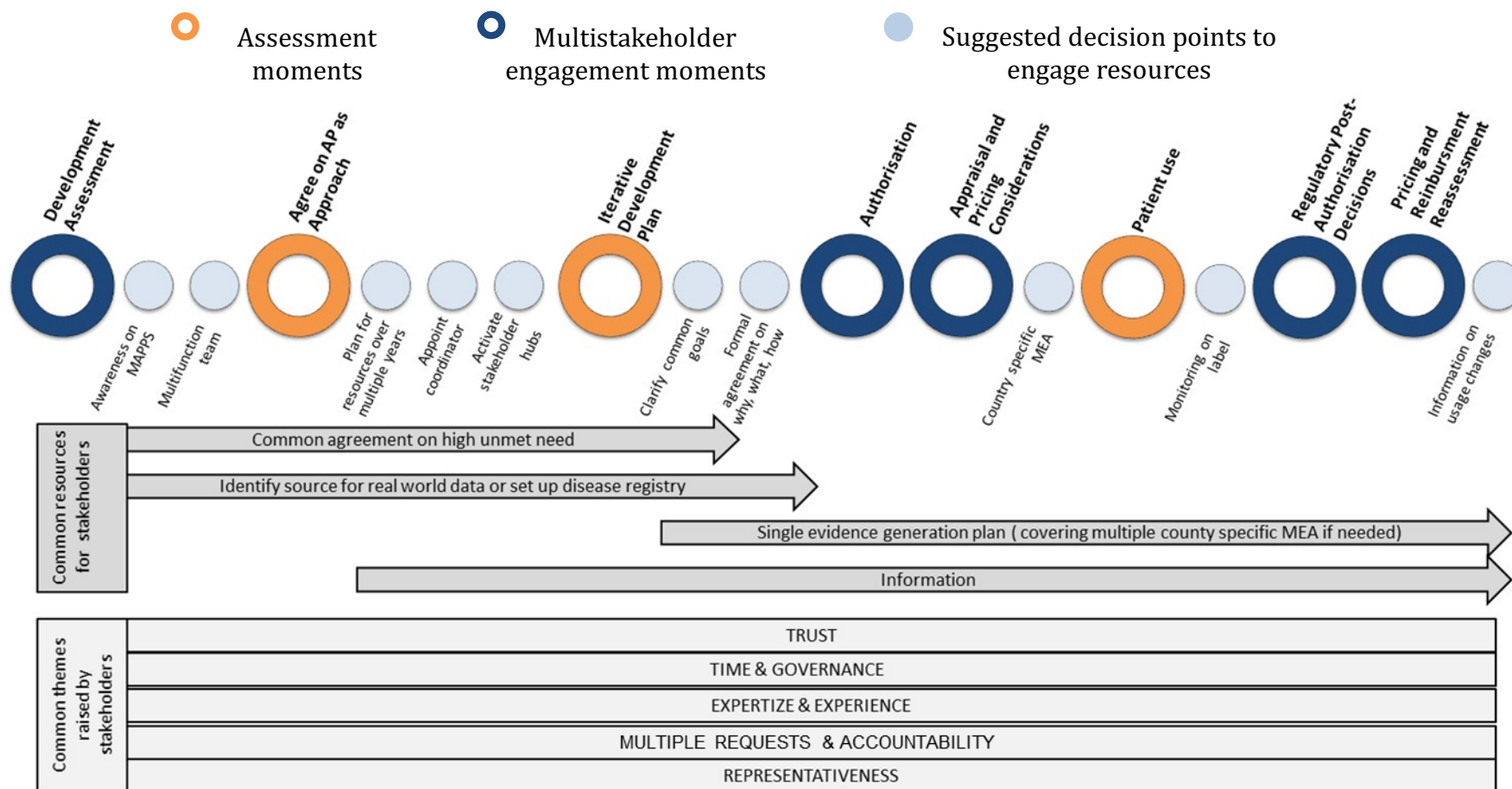


Figure 1 Schematic depiction of the key Assessment and Multi-stakeholder engagement moments of the Seamless Pathway against stakeholder resource requirements to engage with, and act upon, decision making. Both common resources and common themes raised by all stakeholders are depicted (grey boxes and arrows). Key Assessment moments (orange circles) and Multi-stakeholder engagement moments (dark blue circles) of the Seamless pathway, are depicted in addition to numerous other moments (small light blue circles) where stakeholder specific resources need to be understood and engaged.

It is expected that stakeholders might disagree in good faith and disengage from MAPPs. However, this is not without consequences for the other stakeholders - there should be a clear rationale with adequate methods in place for conflict resolution, and a mechanism to disengage from MAPPs.

5.1.4. Time, human resource and organisational governance

It is critical for each organization to consider how their role in MAPPs fits within their current mission and processes. Ultimately whether the organisation has the mandate and desire to be involved with certain aspects of MAPPs will dictate the allocation of resources for this type of activity.

Greater clarification on the likely number and frequency of interactions between stakeholders over a medicine life cycle was requested, as this was seen as the primary driver of resources needed - this will however likely vary from product to product, as well as the number of medicines going into an adaptive pathways route. The conceptual design of the seamless pathway does not, at this stage, allow quantification of the time commitment expected from each stakeholder entering MAPPs.

As the MAPPs process becomes more firmly established, a project manager at a European level should be appointed to orchestrate the different flows of information and interactions, and to act as a point of contact for all stakeholders. The dedicated personnel would have a clear remit for brokering discussions between stakeholders. The exact nature, remit(s) and decision making powers of the project manager proposed here needs further deliberation.

5.1.5. Specific expertise and experience

Stakeholders recognized that taking an active part in any multi-stakeholder engagement moment requires specific expertise that they might not possess internally - especially when the organisation is small (e.g. some patient organisations, SMEs, and competent authorities in smaller member states), or are new to this type of engagement. It is likely that a MAPPs engagement moment will be a place where innovative solutions will be brought up for discussion and experts might be invited to give forward-looking advice across a number of expertise areas. There will also be a need to generate practical experience to make MAPPs a learning process.

Three broad categories of critical expertise were highlighted;

- Science: Disease and product-specific knowledge
- Processes: Understanding of MAPPs concept, regulatory tools (such as parallel scientific advice and conditional marketing authorisations), pricing

and reimbursement mechanisms, cost effective assessment, managed entry agreements, and prescription control tools and measures

- Methodologies: Clinical trial design, data analysis, real world evidence generation, small population studies

Acquiring this critical expertise in-house would partly have to be established through specific education and knowledge exchange.

5.1.6. Number of available experts and accountability

Multiple requests addressed to a limited pool of available experts will further create dilemmas for organizations that will either need to find a way to expand their pool of experts or might have to limit their participation at some chosen moments in the process.

It is envisaged that initial development planning discussions would likely begin as informal, safe harbour interactions, and progress into MAPPs would correspond with more formal interactions and structured agreements, such as through an EMA and HTA scientific advice (SA). Each stakeholder's accountability, when giving input and recommendations during the various engagement moments, requires careful consideration; to be open enough to promote trust and commitment, yet robust enough that accountability for decisions made and resources mobilized at any given point can be upheld.

5.1.7. Stakeholder representation

The seamless pathway describes five categories of stakeholders that will need to interact throughout the drug development process, to support an effective iterative development plan that will span the entire drug life cycle (Patient and Patient Organizations, Healthcare Professionals, Medicine Developers, Pricing and Reimbursement authorities and Regulators).

There are countless distinctions and nuances possible between stakeholders that have been grouped together in one single category. Stakeholders will be differently structured organizationally; they may be individuals or institutions and will have different remits and missions both within, and between, member states and across therapeutic areas.

The challenge is for an individual stakeholder to present a collective view that is specific enough to inform decisions at an early stage, yet remains representative of their broader, generic stakeholder group. Patient organisations have developed engagement with the EMA through the "patient and consumer working party", or with Pricing and Reimbursement authorities (for example in Scotland with the PACE process) - they are the stakeholder most familiar with this challenge and how to manage it.

5.2. Questions raised by a specific category of stakeholder

5.2.1. Patient and Patient organisations

Patient literacy across the entire value chain and in the MAPPs process itself is required for full, consistent, and valuable engagement and involvement in the decision making process. In some cases, a barrier to engagement is language and terminology - even more so than specific expertise. Patient representatives require access to specific knowledge, particularly in clinical development and regulatory processes, and a clear understanding of technical and scientific language.

Disease-specific expertise can come from a greater consolidation of best practices across current initiatives and umbrella organisations, in combination with developing and implementing a framework for obtaining new or greater patient engagement in the medicine lifecycle development.

Patient organisations (so far) are voluntarily involved and not bound by commitments. It will be challenging for patients involved in MAPPs to manage accountability towards their peers, and if the views they represent within the MAPPs process lead to an outcome that is seen as being at odds with patients' best interests (for example when other stakeholders disagree and withdraw), direction from similar initiatives' best practices should be taken into account.

The ability to mobilize resources also requires dedicated funding to ensure "professionalization" of the patient representatives. Adequately covering financial support for recurrent activities could come from public monies or from a fee-for-service.

5.2.2. Healthcare professionals

Health care professionals (HCP) are expected to contribute in the MAPPs engagement moments and in the medicine development in a similar way as the SAG (Scientific Advisory Group) currently does. Scientific societies could encourage a 'MAPPs investigator hub across scientific societies' – a network of HCP who would be pioneers in the MAPPs process – and add relevant expertise and opportunities for cooperation between experts. It is anticipated that MAPPs will also solicit resources at the point of care beyond current general capacity. As is the case today, at the point of care, HCP are responsible for post-Marketing Authorisation data collection to fulfil the requirements of, for example, the Conditional Marketing Authorisation. Medicines authorised under MAPPs would be expected to be on the

list of medicines under enhanced monitoring identified by a black triangle symbol on the SmPC.¹¹

This enhanced monitoring will require additional time and personnel resources to ensure continuous and up-to-date information is conveyed to patients, and additional monitoring and adverse event reporting. Managed entry agreements, including targeted prescription mechanisms and real world data collection, will further add to the administrative burden of the treating physician. Mechanisms to further incentivise HCP and patients as to the importance of continued, structured RW data collection is vital in the context of MAPPs. European Reference Networks might play an important role in cross-border collaboration on data collections and technology where possible (i.e. electronic health records, wearable technology) through maximising available resources and reducing individual burden for the HCP.

5.2.3. Medicine developers

As an initial activity, the medicine developer assesses the degree of unmet medical need, what would constitute value for the different stakeholders, and the value proposition of each potential medicine. To prepare for MAPPs involvement, developers should gather input from various sources and stakeholders on, for example: severity of disease, unmet medical need, disease and treatment pathways, regulatory and evidence requirements, regulatory therapeutic guidance and tools, and pricing and reimbursement authorities' data interests. These initial activities are at the discretion of the developer as they start to elaborate a development plan. Each medicine developer will be organised differently, but typically, most do not assemble a multidisciplinary team so early in the development process when a lot of product attrition still occurs. Compared to existing processes, the earlier and continuous iterative nature of multi-stakeholder engagement moments across the life cycle of a product will likely require an earlier and more intensive mobilisation of resources and experts for the preparation of documentation to support the iterative dialogue.

With a greater input from pricing and reimbursement authorities, patients and HCP in particular, dossiers would need to be in both technical and lay terms and might need to include EU languages other than English.

¹¹

http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000365.jsp&mid=WC0b01ac058067bfff

In this case, resources for medicines developers will expand to include earlier and additional clinical and RWD generation skills in the development teams, as well as data analysis and manpower for recurrent dossier submissions.

5.2.4. Pricing and reimbursement authorities

In most countries, pricing and reimbursement authorities are not typically involved in the medicine lifecycle development until post-Marketing Authorisation discussions (although a number of HTA bodies have been involved in early advice initiatives). More frequent and systematic involvement of pricing and reimbursement authorities in early dialogues and iterative cycles of development may require a genuinely new set of capabilities, skills and processes, and significant increase in dedicated resource compared to the standard process seen today. New scientific and disease-specific knowledge resources would need to be acquired and mobilized across competent bodies. Currently, pricing and reimbursement authorities in small sized countries have very limited capacity to be involved in activities at the European level beyond their current mandate.

5.2.5. Regulators

While scientific advice and conditional marketing authorisation are tools used by regulators, it was clear from the EMA's adaptive pathway pilots that the iterative nature of multi-stakeholder dialogues was resource-intensive and required a dedicated coordinator to manage the multi-stakeholder dialogues and submission/evaluation processes. Like other stakeholders, regulators must carefully consider the amount of information required for MAPPs regulatory assessments.

6. Recommendations and options for future work and next steps

The proposed conceptual adaptive pathways framework¹² presents a series of critical decision-making points along the development pathway, where multi-stakeholder interactions will require dedicated resources. Experiences of stakeholders involved with similar initiatives, existing expertise within each involved institution/organisation, and resource governance, play a role in determining what additional resources would be required in order to engage effectively in MAPPs. What we present here are a series of recommendations aimed at supporting

¹²

http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2017/07/WC500230414.pdf

stakeholders in their reflection on how to access resources to effectively participate in the multi-stakeholder interactions¹³.

The recommendations presented in this document should always be read in combination with the seamless pathway report (D2.05) - as it builds on the MAPPs moments identified in that document. However, the exact nature of the resource needs is, as yet, an unknown, and is not possible to quantify at this early stage of the MAPPs conceptual development.

To fulfil some of the resource needs expressed by stakeholders (see section 5) to engage in multi-stakeholder MAPPs moments, we recommend to:

1. Identify and pilot methods (see 5.1.1) - inclusive of all stakeholders' point of view - to support the MAPPs engagement and test the feasibility of the engagement criteria. The use of MCDA (multiple criteria decision analysis) in this case could be very fitting. The pilot will also help clarify whether further work is needed to harmonize stakeholder's interpretation of the criteria (including unmet need) in a specific development context.
2. Make available an **inventory of registries** that are accepted data sources (5.1.2, 5.2.2) in support of MAPPs.
3. A concordat or non-binding agreement between all involved stakeholders, setting out stakeholders' common ground and specific expectations (see 5.1.3), commitments to produce data, documents, time, expertise and effort, would go a long way to solidifying the trust between stakeholders and ensure the success of MAPPs. This would include mechanisms for initial engagement (safe harbour), templates for conflict resolution, and mechanisms of disengagement in the decision making process.
4. A **support and development platform** for stakeholders involved in MAPPs - involving experienced individuals that act as coach, mentor and mediator - that could sustain accurate and continual transfer of knowledge and experience to other stakeholders (hub and spoke model of learning). (see 5.1.5, 5.1.7, 5.2.1, 5.2.4 and 5.2.5) Such models are widely used in healthcare and could span geographical boundaries, and facilitate wider involved learning and acceptance to Eastern European Member States. One possible solution might be an explicit agreement between pricing and reimbursement authorities to use a pool of advisors, where each specializes in a particular disease area or methodology.

¹³ As described in the seamless pathway and engagement criteria documents

5. **Resource planning** (see 5.1.4) can be derived in part from estimations for time and personnel, from initiatives where multi-stakeholder interactions have been piloted, and where structured dialogues occur over several iterations (meetings, feedback, resubmissions), and over a number of months – such as Adaptive Pathways pilots, MoCa and joint EMA-EUnetHTA initiatives.
6. Define a process to prioritize potential MAPPs candidates, to limit the number of products per year (initially at least) – stakeholders need a reasonable notice period in order to plan ahead for dedicated resources and timely input over multiple years. (see 5.1.4) The MAPPs engagement criteria (D2.03) will assist developers in self-selecting only the most relevant candidates to take through an adaptive pathway.
7. Seek **political support for MAPPs concept** (see 5.2.1 and 5.2.4) in order for member states to allocate the requisite resources to hire and develop experts. As noted in the introduction, while the remits of each stakeholder remain, the stakeholders that might most need new resources were considered to be pricing and reimbursement authorities, patients, and healthcare providers (HCP). This is also critical to be able to implement recommendation 4. One enabler for gaining broader political support might be funds to undertake a few MAPPs pilots.
8. Provide a **platform and framework to enhance patient engagement** across the medicine development chain - that accounts for diverse patient populations and marginal sub populations. Increasing patient literacy and knowledge in key areas of medicine R&D (see 5.2.1), refining the value of the shared mutual patient centricity goal (see 5.1.1 and 5.1.3), and managing conflicts , will contribute to more structured and relevant patient input (see 5.2.1). Existing efforts through, for example, the EUPATI initiative, could be leveraged to include MAPPs-specific training and knowledge brokering, alongside greater use of existing resources from the PCWP networks to support implementation.
9. Several initiatives, for example EMAs Parallel Scientific Advice, MOCA and the UK's EAMS, have strived to make an efficient resource utilisation to **avoid duplication** between stakeholders, by aligning timetables and agreeing on using single dossier submissions (see 5.2.3 and 5.2.4) where possible. The practical lessons derived from these initiatives should be integrated when formalizing detailed processes for MAPPs. At the same time, the need for a dedicated MAPPs project manager to orchestrate the different flows of information and act as a point of contact for all stakeholders should be considered. (see 5.1.4, 5.1.5 and 5.1.7)

7. Conclusion

In conclusion, for an adaptive pathway to become an operational multi-stakeholder route for medicine development, we recommend to further explore 3 key components:

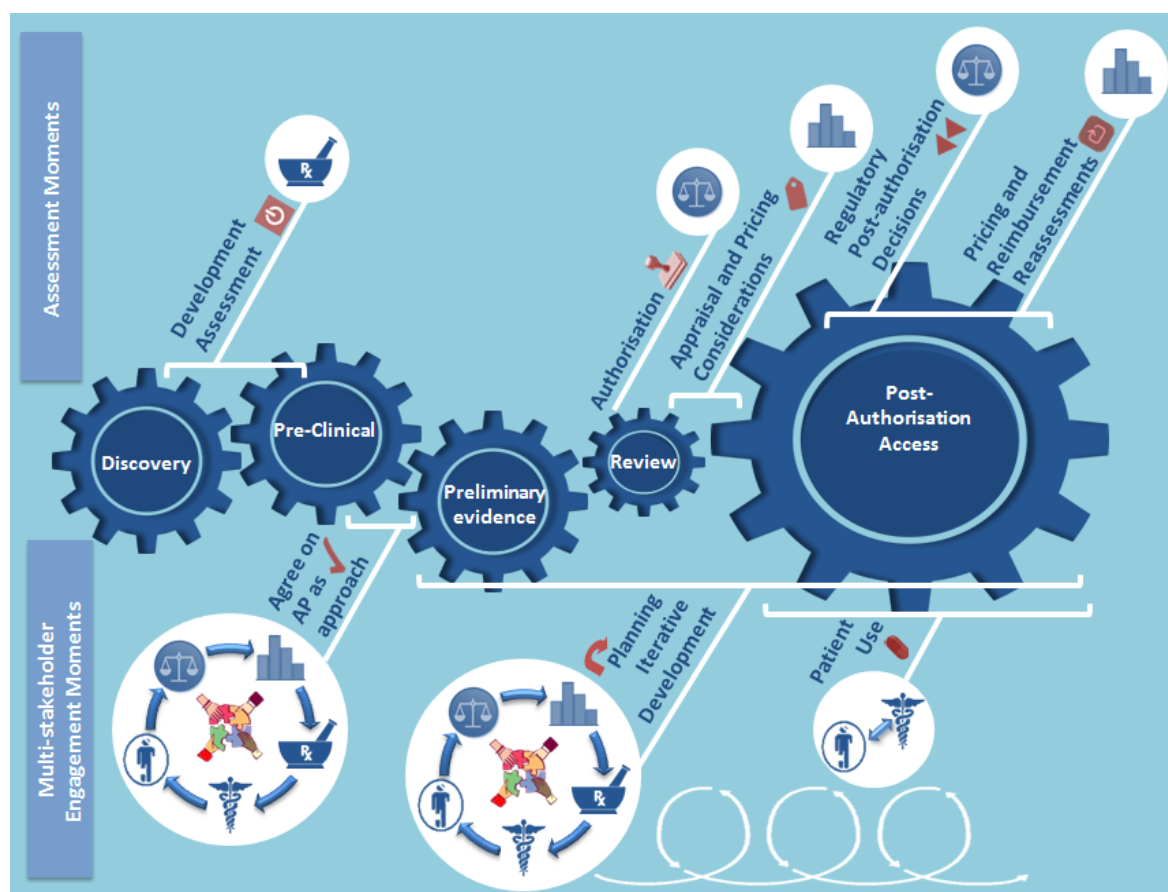
1. The “political” mandate for stakeholders in member states to engage in some sort of advisory role to enable patient-centred medicine development is needed. The conditional marketing authorisation tool, additional (data) monitoring procedures, and the progress made in scientific advice with the early dialogue working parties at the EMA, are mechanisms that are supportive of MAPPs implementation. MAPPs specific processes and procedures can be further expanded from this current foundation, if all stakeholders are willing to and able to engage around the same patient-centric goal.
2. The need to have access to new core expertise is central to all stakeholder engagement in MAPPs. Leveraging existing overarching platforms to streamline resources and expertise seems the most practicable and reliable way to advance with MAPPs capacity-building for all stakeholders. Examples of platforms to either model from or contribute to a MAPPs hub are EUPATI, the patient and consumer working party at EMA (PCWG), the scientific advisory groups (SAGs), the scientific advice working party (SAWG), EunetHTA and also potentially the MEDEV, European Reference Network and scientific societies.
3. Building trust between stakeholders requires a common goal balanced against each stakeholder’s interests. Further research should explore opportunities and methods on how to ensure stakeholders execute, over time, on their commitments without being bound by requests that turn out to be unreasonable or unfeasible. Safe harbour discussions have demonstrated a certain level of implied trust between stakeholders which could be further formalized through a type of research concordat. The degree(s) to which advice/commitments is binding or non-binding under such a concordat needs to be explored carefully to reflect each stakeholder’s accountability.









The recommendations in this paper focus on enabling the multi-stakeholder engagement and decision moments in MAPPs, and highlight the fact that next to the in-depth expertise needed by each stakeholder, there is an opportunity to develop trust and build soft skills to allow stakeholders to develop an advisory role and increase their impact.

APPENDIX A

Schematic and explanatory table of the Seamless Pathway (From D2.05)

Each product life-cycle phase is symbolised by a blue cog, in the below diagram. Each cog is sized comparatively to represent the characteristic duration of the phase during the lifespan of a typical medicine. The top half of the diagram includes the 'assessment' or 'decision' moments by the stakeholder represented. Within the bottom half of the diagram, moments of 'multi-stakeholder engagement' are represented.



	Adaptive Pathway Moments	Description of the Process Steps and Decision Points
	Development assessment	Prior to the medicine developer making a decision for a product to enter development, the developer assesses the opportunity of a potential medicine, for example, considering general input and/or guidance from various stakeholders.
	Agree on adaptive pathway (AP) as optimal approach	Based on the engagement criteria, stakeholders offer a collective, documented decision under “safe -harbour” discussions regarding their agreement to progress with an adaptive pathway engagement approach for a particular potential medicine.
	Iterative development plan	<p>An iterative development plan is an evolving product development strategy proposed by the developer and adapted through multi-stakeholder engagement. The evidence generation plan is discussed among the stakeholders and takes into consideration the critical questions to be addressed preliminarily in order to also support subsequent pricing and reimbursement decisions at the national level. The iterative development plan is unique and extends over a significant period of time (and likely iterations) supporting an adaptive pathway from the beginning to the end. Evidence generation may involve multiple clinical trials, single-arm studies or a single Phase 2 trial or RWE depending on the specific product.</p> <p>For example,</p> <ul style="list-style-type: none"> • A given plan considers the evidence generation commitments and follow-up measures for a conditional marketing authorisation (CMA), for pharmacovigilance and/or new studies to expand the patient use. • It should also consider the post authorisation evidence generation measures necessary to meet the pricing and reimbursement requirements and an agreement on the timelines for review and reassessment.
	Regulatory authorisation	Regulatory decision to authorise a medicine for patient use in a given therapeutic indication(s).
	Appraisal and pricing considerations	At the EU level, considerations for the pre- as well as post-authorisation data collection plan take place prior to authorisation as a component of the iterative development plan. At the national level, discussions on pricing and reimbursement follow regulatory authorisation and reflect the iterative development plan.
	Patient use	The foundation for an adaptive pathway concept is to provide patients who experience a high unmet medical need with an initial or improved treatment option through tools to enable on-label prescribing. In parallel to an adaptive pathway, patient use may also comprise further clinical trials programs as appropriate.
	Regulatory post-authorisation decisions	<p>Regulatory decisions are also taken during the post-authorisation phase. For example, regulatory decisions may lead to:</p> <ul style="list-style-type: none"> • widening or contraction of the marketing authorisation, e.g., in terms of eligible treatment population, or • reinforcement of safety measures, or • granting of a full marketing authorisation from an initial CMA, or • authorisation of a new indication with or without follow up measures .
	Pricing and reimbursement reassessments	Predefined moments when decisions on pricing and reimbursement by national authorities are reviewed. The conclusion of the reassessments may trigger potential adjustments of reimbursement or price conditions at the national level. As an example, a negative reassessment could lead to the end of reimbursement for the indication in scope.

APPENDIX B

Engagement Criteria (from D2.03)

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?*

APPENDIX C

Table of partners who contributed to this work

University of Oxford (CASMI)
Sanofi Genzyme
Amgen
BMS
Lysogen
Merck/MSD
Novartis
Roche
EFPIA
EURORDIS
EMA