Enablers of decision making in an adaptive environment: managing uncertainties and disengagement

October 2017

The work leading to these results was conducted as part of the ADAPT SMART consortium (Accelerated Development of Appropriate Patient Therapies: a Sustainable, Multi-stakeholder Approach from Research to Treatment-outcomes). For further information please refer to www.adaptsmart.eu. This paper is the result of the collective input from working group D3.03 and only reflects the views of the authors.

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115890. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.

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ABREVIATIONS

MAPPs	Medicines Adaptive Pathway to Patients
ADAPT-SMART	Accelerated Development of Appropriate Patient Therapies: a Sustainable, Multi-stakeholder Approach from Research to Treatment-outcomes
HCP	Health Care Professional
IMI	Innovative Medicines Initiative
MA	Marketing Authorization
MS	Member States
HTA	Health Technology Assessment
DHPCs	Treatment guidelines and Direct Healthcare Professional Communications
ERN	European Reference Networks
RCT	Randomised controlled trial
RWE	Real World Evidence
SA	Scientific Advice
EuNeHTA	European Network of HTAs
IP	Intellectual Property
P&R	Pricing and Reimbursement
MOU	Memorandum of Understanding
AA	Accelerated Assessment
CHMP	Committee for Medicinal Products for Human Use

EXECUTIVE SUMMARY

The development of the Medicines Adaptive Pathway to Patients (MAPPs)[1] concept as a mechanism of appropriate early access of innovative medicines to patients with a high unmet medical need, centres on the application of this concept within the existing regulatory and legal frameworks. MAPPs addresses the evidence vs access conundrum through a progressive reduction in uncertainties as more evidence is generated over time informed by iterative multi-stakeholder dialogue and assessment. For a product to utilize MAPPs it must fulfil six criteria. During iterative cycles of development, multi-stakeholder consensus is sought at key engagement points. Under MAPPs, each stakeholder and decision maker retains their remit and responsibility - the regulators and payers, for example, as decision-makers will retain full ownership for granting/ withdrawing marketing authorization or granting/withdrawing reimbursement based on their assessment.

MAPPs requires stakeholders to engage in a common dialogue during the development process to define which evidentiary uncertainties to address. The early and continued dialogues create a moral obligation for stakeholders to complete the process and to inform each other from the decisions taken. This collective engagement whether formalized or not raised discussions amongst stakeholders on "exit strategies" meaning their ability to disengage or reverse previous decisions and to manage the impact of a negative opinion or potential product withdrawal.

We have found that the terminology surrounding disengagement from MAPPs needs further clarification as interchangeable terminology such as, 'exit strategy', 'withdrawal', or 'disinvestment' holds different meanings and different implications to different stakeholders.

Flexibility remains important and it is not possible or even desirable to map all the potential scenarios under MAPPs where disengagement may occur. Many will be specific to a product or a therapeutic area. We have sought to consolidate an understanding, but not seek consensus, across various ADAPTSMART deliverables on the rationale why disengagement from MAPPs might occur, how it may impact stakeholders and where gaps exists for stakeholders. We identified two important gaps ; i) the lack of established best practices to manage price adjustments based on the level of evidence (mainly for pricing and reimbursement authorities) and ii) despite the fact that there is no MAPPs designation, the lack of an established process of how to concretely disengage and how to effectively manage the impact such decision has on

[1] It is important to keep in mind that MAPPs follows the existing frameworks and seek through multistakeholders engagement to optimize the timelines for development. MAPPs as of today is not a formal pathway and does not have formal entry or exit points. We describe with MAPPs a virtual umbrella encompassing all stages of development, assessment and approvals optimized for early access.

other stakeholders. The later could be specified in an overarching agreement that would accompany the development process and covers topics such as the binding or non-binding nature of dialogues, stakeholder duties and expectations, a mechanism for conflict resolution or arbitration, and best communication practices. We provide a summary of discussions around these topics to stimulate further exploration as the MAPPs concept matures.

1. INTRODUCTION

ADAPTSMART is a multi-stakeholder consortium that was set up as a *Coordination and Support Action* under the EU Innovative Medicines Initiative 2. The Innovative Medicines Initiative (IMI) is Europe's largest public-private initiative aiming to speed up the development of better and safer medicines for patients. IMI supports collaborative research projects and builds networks of stakeholders in order to stimulate pharmaceutical innovation in Europe.[2] The ADAPTSMART consortium comprises all relevant stakeholders in the healthcare ecosystem: patients, academics, healthcare-providers, the research-based pharmaceutical industry, regulators, and health technology assessment (HTA) bodies. Some EU payers and payer organisations also engaged in constructive dialogue with the consortium. The objective of ADAPTSMART is to establish an enabling platform to initiate a dialogue with relevant stakeholders for the coordination of Medicines Adaptive Pathway to Patients (MAPPs)-related activities.

MAPPs is conceptualized as a development strategy that proactively considers a life-span approach with a focus on enabling appropriate early access for a defined and limited patient population with a high unmet need. A MAPPs development therefore optimizes, through multi-stakeholder dialogues, the use of existing tools that are embedded within the existing EU regulatory, legal and pricing and reimbursement frameworks. Stakeholder's mandates, roles and remits remain unchanged.

The conceptual pathway has been developed at a broad, centralized level, specifying key stakeholder decision points for development, authorization and pricing and reimbursement as well as key MAPPs multi-stakeholder engagement moments [3]. The specificity of MAPPs is that it covers the entire pre- and post-MA development phases of a product. For a candidate product to go through MAPPs all major stakeholders must reach consensus on a set of **six** questions also named **Engagement criteria.**(**Figure 1**).

[2] http://adaptsmart.eu/

[3] ADAPT SMART report D2.05 "Seamless Process and Decision Points of an Adaptive Pathway" (June 2017)

Figure 1: Framework of questions to be addressed by stakeholders when considering MAPPs

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?

There is no new 'MAPPs designation' proposed or preference given to the use of this pathway. Stakeholders nevertheless wondered what impact early and repeated multi stakeholder engagement will have on their ability to revisit previous (conditional) decisions in the light of new information as the evidence base evolves pre and post marketing authorization for a given product. Pragmatic arguments have been made about the difficulty to reverse previous decisions, and skepticism exists about effective and reliable Real World Data collection and prescription control mechanisms. In this respect it was considered important for the acceptance of the adaptive pathways framework to further explore engagement criteria question 4# and the mechanism(s) that could be used in case the product does not meet requirements and/or expectations. The question 4 specifically mentions 'strategies for payers' but is actually relevant for all stakeholders

1.1 Managing Uncertainties

Within the MAPPs concept, stakeholders' remits and decision making capabilities won't change compared to the pathway in use today, thus stakeholders' have a suite of existing tools and processes at their disposal in order to manage what they consider as key uncertainties. For example, regulators may request post-marketing studies or risk management plans, restrict the indication(s), issue warnings and in extreme cases withdraw a marketing authorisation.

To manage uncertainties related to effectiveness or economic value, and depending on their national specificities, pricing and reimbursement authorities can renegotiate prices, set price volume agreements, define reimbursement criteria and to an extent control prescription behavior. It is expected that in the specific case of MAPPs Health Technology Assessment bodies (HTAb) will require additional evidence generation which could be used for outcomes-

based MEAs. Such MEA could both facilitate patients to have early access to the treatment and support product per product workable strategies for payers in case the product under-performs [4]. Medicine developers may choose to change the development pathway by opting out of a process or withdraw a product from the market.

In summary, in the context of MAPPs as in other development contexts, stakeholders want to understand their options when something is not going as expected. Neither do they want in MAPPs to be bound to a resource consuming process when the process has outlived its usefulness and ceases to add value. Stakeholders want to be protected against other parties failing to meet their commitments and wish to enforce corrective actions if a product performs differently than what was initially expected. This paper is set to explore these issues on 'disengagement' or 'exit' in more detail.

2. OBJECTIVES

Despite the lack of a formal pathway entry or MAPPs designation a mechanism or strategy to disengage (or exit) from MAPPs has been a recurrent theme across many of the ADAPTSMART working groups. For each stakeholder the term 'exit' raised different concerns related to their existing mandate. It is therefore not our intention to seek consensus on the matter. In this paper we expose the different meanings identified for 'exit' or 'disengagement' strategies with the objective to describe gaps for stakeholders to consider in the context of their engagement with MAPPs. These were as follows:

1. Agreement on the use of the terminology for disengagement.

We set out to present here a factual summary of known **terminology**, a high level overview of what disengagement (or exit) means to each stakeholder group as it is today, considering the specific remits and processes that they are involved in. Based on this we analyse potential gaps in the adaptive environment.

2. Agreement on common scenarios for corrective action.

We explored some **common scenarios** under MAPPs where corrective action may be needed or when additional information may lead to revisiting a previous conditional agreement. It is not possible to map all of the many potential reasons why this may occur. A detailed seamless pathway will need to ensure tools are in place for stakeholders to adequately manage unexpected situations.

[4] ADAPT SMART report D3.05/D3.07 "Managed Entry Agreements for Pharmaceuticals in the Context of Adaptive Pathways in Europe" (March 2018)

3. Agreement on potential gaps to enable informed decision making.

We suggest a list of questions that are common to all stakeholders that should stimulate further discussions as future clarity is reached on key MAPPs themes such as managed entry agreements (MEA), decision making, prescribing in targeted populations, and member states specific transferability of ADAPT SMART recommendations.

3. METHODS

We firstly compiled an inventory of the use of the term 'exit', 'withdrawal', 'disinvestment' and 'disengagement' used by stakeholders during the many ADAPT SMART discussions and deliverables, and in the literature when relevant to the context of adaptive pathway.

Based on this inventory we highlighted some recurrent themes, which we discussed with stakeholders to consolidate their opinions. We then examined a few classical "failure" scenarios as they could normally occur in drug development and examined how stakeholders could handle the situation within MAPPs. The findings are described below.

4. FINDINGS

It is important to keep in mind that MAPPS follows the existing frameworks and seek through multistakeholders engagement to optimize the timelines for development. MAPPs as of today is not a formal pathway and does not have formal entry or exit points. We describe with MAPPs a virtual umbrella encompassing all stages of development, assessment and approvals optimized for early access.

4.1. Use of terminology

The term, 'Exit strategy' has been a recurrent theme across many of the ADAPT SMART working groups. Stakeholders have expressed the need for guarantees that products entering an adaptive pathway will comply with the selection criteria and with all the requirements agreed upon throughout the product lifespan including a controlled patient use in clinical setting.

Since a MAPPs lifespan approach for a product will likely span many years of pre- and post-marketing authorisation and cover several cycles of evidence generation and (re)assessment an "exit" could eventually occur in a number of situations.

Moreover the meaning, the trigger and modalities of an exit strategy differs according to the stakeholder accountability and remits. For example, in the context of a regulatory pathway (e.g.

PRIME scheme and conditional marketing authorisation) the word ‘exit’ was mainly used to refer to the lack or loss of eligibility for the specific regulatory process.

The word ‘exit’ was also used as a synonym of market withdrawal whether for safety, commercial or other reasons. In these cases the implications for patients and prescribers in terms of treatment continuity and the information on the modality of the withdrawal would take center stage in the strategy.

In the context of healthcare funding the word ‘exit’ however was linked to the management of low – value of a therapy to the healthcare system. In this case total withdrawal of access or reimbursement is challenging. Exit strategies are calling then for negotiated managed entry agreements, effective off label use control, adapted pricing schemes, and/or communication strategies in case of reimbursement withdrawal.

None of these situations are specific to MAPPs however, it is expected that early access will increase uncertainties in decision-making at the early stages. Stakeholders assumed that disengagement decisions occurring later in the process after reimbursement and wider access has been granted might become more frequent. A greater emphasis on a continuous generation of evidence over the lifespan of a product and the increased interactions between stakeholders made also clear that MAPPs will require, from the beginning, a clear engagement from decision makers to discuss the type and level of evidence expected at the different stages of development. The multi- stakeholder engagement moments, where the different stakeholders meet to discuss their requirements ahead of time, is a critical component of the process. It is also the moment to discuss the practical challenges, to evaluate the feasibility of some strategies and to agree on the adjustments to be made in the light of emerging evidence and predict how they might impact the involved stakeholders (figure 2). These multi-stakeholder moments may also involve a decision to discontinue support (by one or more stakeholder(s)) triggering another type of disengagement from MAPPs. Communication between stakeholders and agreements how these decisions should be implemented to minimize the impact on patients care are critical.

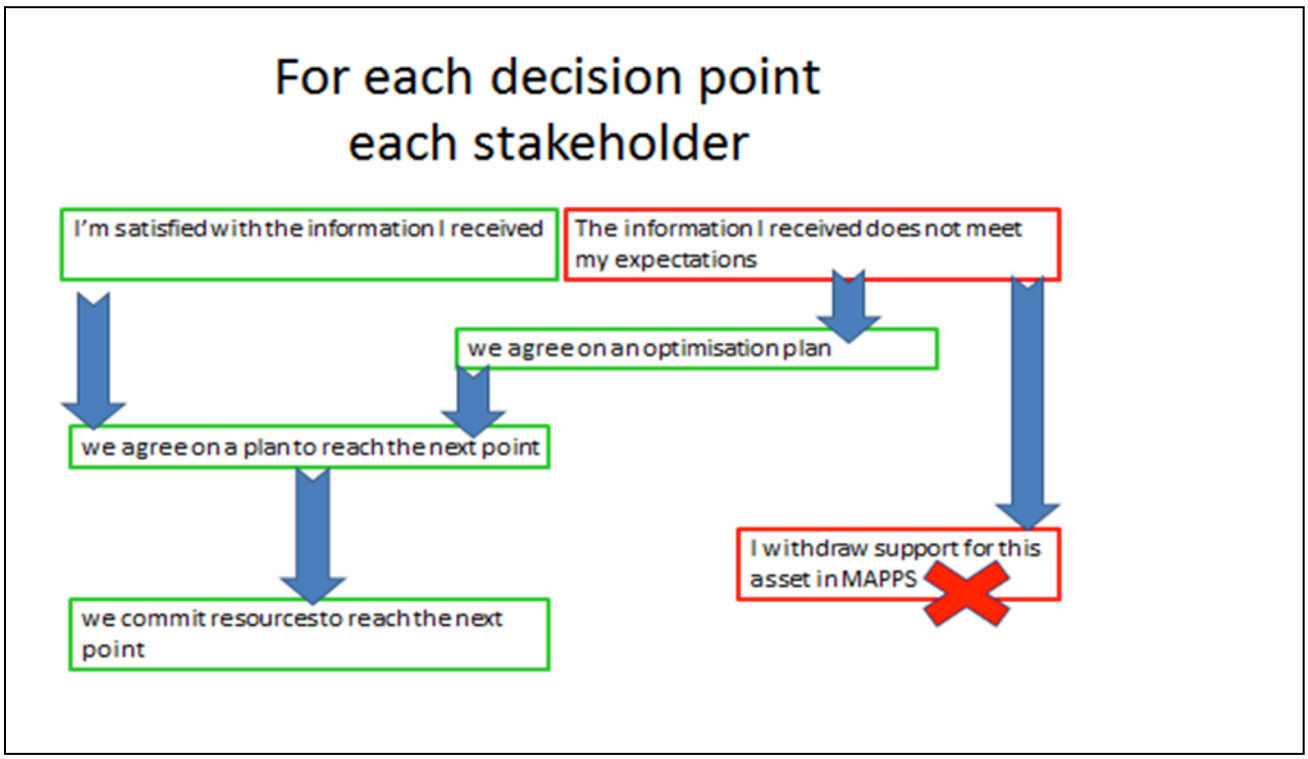

Figure 2. Simplified schematic of the likely decision process of each stakeholder at each multi-stakeholder engagement moment in the seamless pathway. Consensus is needed from all stakeholders to commit resources to reach the next engagement (decision) point.

4.2 Scenarios Under MAPPs

We broadly recognize three reasons for disengagement based on a stakeholder's own assessment and resulting in different scenarios and contingency plans to be implemented through MAPPs (recognizing there are many other possible variants on these that are not practical to map out here):

1. An unacceptable safety risk resulting in the termination of the drug development or commercialization

2. Insufficient or disappointing evidence requiring the implementation of a contingency plan to realign expectations and findings including label restriction or withdrawal of access in some cases. It is to note that pricing and reimbursement authorities are operating at national level and that therefore disengagement strategies from payers might be market specific.

3. An ascertainment of inefficient use of resources by a stakeholder leading to reconsider the added value of a MAPPs engagement for a specific product. It should be recognized that when it comes to disengagement regulators, payers and medicine developers are more likely to be

decision makers in one of these above scenarios. Conversely patients, healthcare professionals and medicine developers are the stakeholders most likely impacted by an other stakeholder decision to disengage.

4.3 Current Measures to Disengage

Some examples of current processes where a decision to cease or disengage with that process could occur, are highlighted below to shed light as to the types of mechanisms that are also applicable to MAPPs. In many cases specific legislations and guidance exist on how to notify product withdrawals in the different market.

4.3.1 Regulatory pathways and Post marketing commitments

The existing centralized pharmaceutical legislation[5] foresees the following scenarios:

Based on criteria being met, and stakeholder considerations, it is predicted that only a selected number of products will be developed using the entire MAPPs concept. The full regulatory toolbox would be assessed regularly for appropriate utilization during product development and if after being included in an adaptive pathway a product does not, for whatever reason, meet the MAPPs criteria anymore, stakeholders may decide to advise continuation of the development under the standard pathways.

There are tools available to accelerate the development, assessment and patient access of a medicine in the EU. For example, a medicine developer may apply for an **Accelerated Assessment (AA)** via the EMA- if the candidate product meets the criteria and the application granted, the CHMP will adhere to the accelerated timetable (in accordance with Article 14(9) of Regulation (EC) No 726/2004 for the assessment). If however, during any time during the AA the CHMP considers that it is no longer appropriate to conduct an AA, assessment may be continued under the standard centralized route. Reasons may include major objections that cannot be handled in an accelerated timetable. Similar procedures occur for other tools such as PRIME[6]

In the case of a **conditional marketing authorisation (CMA)**, the specific obligations under that authorisation are also binding and are reviewed on an annual basis. If those obligations to

[5] Regulation (EC) No 726/2004

[6] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000660.jsp&mid=WC0b01ac05809f8439

provide confirmatory data are fulfilled the CMA may be converted to a full marketing authorization, otherwise the CMA remains in place until further confirmatory data is provided. Should the benefit: risk become subsequently unfavourable the license could be withdrawn[7].

The PV legislation provides a legally binding commitment on the marketing authorisation holder to undertake post MA monitoring. Feasibility of an adaptive pathway also builds on the experience gained with the centralized monitoring tools introduced by the 2012 **pharmacovigilance (PV) legislation** (e.g., post-authorisation safety studies (PASS), post authorisation efficacy studies (PAES), and patient registries)[8].

Under MAPPs, agreeing in advance the requirements from each stakeholder should help to increase the relevance of post MA commitments to all stakeholders where expectations regarding safety, efficacy, effectiveness, value, and clinical use are summarized in a single evidence generation plan. Whether these commitments approved by all relevant stakeholders could then be included in the risk management plan mandated by the EMA could be further explored. Companies could do this on a voluntary basis.

4.3.2 Managed entry agreements

A gradient of measures can be applied to manage progressive introduction in a market or disinvestment if the therapy becomes obsolete however the field still lack agreed best practices and methods.

Reimbursement and payer authorities have limited experience today with coverage of a medicinal product with evidence development as a mechanism to manage the entry of a product on the market when significant uncertainties remains regarding the performance of a product (See Managed Entry Agreements D3.05). Experiences reported are limited to a single country, generally do not align with regulatory specific obligations (i.e. a CMA) and do not include multiple stakeholder perspectives. Most managed entry agreements in the EU are currently financed based (i.e. discounts and rebates) and without evidence generation plans. Outcomes-based arrangements (reduction of uncertainty, and budget impact through assessment against agreed outcome measures) are less frequent due to the complexity of the implementation and the lack of infrastructure for data collection. Pragmatic arguments are made highlighting the implementation challenges of such follow up measures and the difficulty in practice to reverse a positive decision, based on emerging unfavourable cost-effectiveness.

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7 http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000925.jsp&mid=WC0b01ac05809f843b

8 http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000491.jsp

Managing the entry of a medicine on the market can also occur via **controlled prescription**, hence medicine appropriate use in real life conditions (i.e. control of off-label prescription, delivery in hospital, or specialist certification). Practices and tools, and the effective impact on prescribing behavior, vary across member state and are designed to suit local health care infrastructures and societal values.

Monitoring tools like disease registries and off-label prescription control will increase awareness of the development status of a product with healthcare professionals, and might facilitate the implementation of a communication plan in case of important changes (such as addressing inappropriate prescription). Stakeholder accountabilities and prescription control tools are being explored under D3.08 and jointly by D2.07 and D3.09.

MAPPs therefore provides the opportunity to facilitate alignment and expectations within the single evidence generation plan which would elicit a reduction in uncertainty of evidential requirements for each stakeholder (e.g. regulators, payers, patients, HCP, etc) as the evidence base evolves. Such a development plan could include a gradient of measures that would be used when managing a product through its lifecycle and foresee contingencies in case of insufficient effectiveness of a product (i.e. controlling prescribing behaviour, price discounts or restricted reimbursement, restricting indications, or removal from the market). The conditions under which patient access to a product may be lost (reimbursement decision, withdrawal of MA, or prescription control) should be envisaged with all stakeholders ahead of time.

Despite the above mechanisms available today, the commitments or ability from each stakeholder to mobilize resources in order to get from one MAPPs multi-stakeholder engagement moment to the next is still uncertain and needs addressing.

4.4 Identified Gaps

Two major gaps emerged from this analysis:

A. The **lack of established best practices** to manage disinvestments and price adjustments based on the level of evidence. This is primarily a concern for reimbursement and payer authorities.

Both theoretical and pragmatic hurdles exist today:

1. How to ensure a mandatory, unbiased, and reliable data collection and interpretation of evidence in the post marketing phase;

2. Lack of trust in outcome based deals and managed entry agreements especially in small populations;

3. How and when to weight evidence and adjust price.

B. The **lack of terms of reference**. For all stakeholders the terms of their engagement and disengagement in MAPPs are unknown. As they are the last in the access decision making chain the lack of a disengagement process was seen as especially troublesome for the payer and reimbursement authorities.

1. How to disengage from a MAPPs process, when, and what happens next?

2. Is there a discrete procedure to follow to disengage from MAPPs? Should there be criteria? Should the rationale for the disengagement be shared with other stakeholders upfront?

3. How to mitigate the impact of that decision on other stakeholders? How does communication occur effectively and in a timely manner? What arbitration in case of disagreement between stakeholders?

5. DISCUSSION AND RECOMMENDATIONS

5.1. Adapt Terminology

During the July 6th 2017 workshop, stakeholders expressed they were not comfortable with the dichotomous nature of the term 'exit' as the term 'exit strategies' tends to imply the total withdrawal of a technology from the market without specifying the rationale , the timing, the specific measures and decision maker's accountabilities. Other terms such as 'optimization strategy' (the implementation of a contingency plan and the decisions taken in accordance to reconcile insufficient evidence with high expectations), and the term 'disengagement' were deemed more appropriate in the context of MAPPs. Thus in line with the proposed criteria for engagement with MAPPs we propose to use the term **disengagement** as the broadest and most appropriate term going forward within this context.

5.2 Document Principles For Stakeholder (Dis) Engagement

At each key **decision point or MAPPs engagement moment** in the lifespan of a product, iterative (re) assessments would occur. This represents pre and post-authorisation decision-making moments where new knowledge is gained and a critical assessment is made against the agreed criteria as whether or not to progress a product along an adaptive pathway. It could be envisioned that pre-authorization agreements by all stakeholders cover fulfilment of the engagement criteria and acceptance of the development plan for the entire lifecycle of the

product in question. Post authorization reassessments would still include multi-stakeholder dialogue, assessing the fulfilment of engagement criteria and also include optimisation strategies - informed by real world evidence to confirm benefit-risk, assess appropriate utilization, and/or demonstrate value – as well as potential adjustments of reimbursement.

The role of the multi-stakeholder discussion in case of disengagement decisions need to be further refined as the primary objective that has brought stakeholders together (to advance the development of a treatment to meet patients need) is vanishing with time. For example, in the eventuality that drug development programs are totally or partially terminated, or products lose funding in a market, patient representatives perspectives need to be taken in account [9]. The patient organisation's support for the rationale will be essential in designing a relevant plan to mitigate the impact on the affected patients and to increase patient understanding of the change.

Stakeholder specific remits and decision making capabilities remain under MAPPs, yet a mechanism by which to initiate and manage those multi-stakeholder discussions is as yet unresolved for MAPPs. Best communication practices between stakeholders should also be further explored. Best practices from current multi-stakeholder dialogues both within the life sciences and outside of it (e.g. manufacturing and business) could be drawn from.

It could be foreseen that an overarching agreement between all stakeholders is acknowledged after preliminary safe-harbour discussions.

For example, an overarching agreement that documents the various understandings reached by stakeholders, the binding or non-binding nature of the advices, the commitments, the stakeholders' duties in term of communications and the mechanism for conflict resolution or arbitration, could prove to be facilitatory to support MAPPS in the long term.

The recent **adaptive pathways (AP) pilots**[10] at the EMA did have eligibility criteria that had to be met per candidate product, in order to justify multi-stakeholder dialogue and resource commitment from other stakeholders. The process of multi-stakeholder dialogue in these pilots was however non-binding (safe harbour). Due to the ongoing nature of these pilots no disengagement (or exit) criteria have been enlisted yet, but this would be expected in the future. Close attention should be paid here to transfer learning to MAPPs.

Under any type of agreement the mechanisms for disengagement and rules for arbitration should be specified. While the individual stakeholder specific component obligations remain binding (e.g. fulfilment of regulatory requirement for MA including pharmacovigilance) the

[9] ADAPT SMART report D3.08 "Ethical and Legal Aspects of Adaptive Decision Making" (October 2017)
[10] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp

degree to which these types of overarching agreements are binding or legally enforceable remain undefined at this stage. The development of any templates or framework requires careful consideration. Additionally, ownership and management of such an agreement needs further consideration as that has implications for enforceability and ultimate accountability.

6. CONCLUDING REMARKS AND OPTIONS FOR FUTURE WORK

We present here a factual summary of known terminology around disengagement and exit, a high level overview of what disengagement means to each stakeholder group as it is today, considering their specific remits and process that they are involved in, and what tools they have respectively to enact this. We include some of the implications to consider when disengaging from MAPPs. This paper aims to stimulate further discussion and clarity as to the key components required to enable disengagement from MAPPs in the best conditions for all stakeholders, which should be taken alongside the **engagement criteria** and **seamless pathway**. Here, as highlighted in both these documents, we present high level ideas which would need to be refined further as MAPPs evolves and will need to take in consideration member states specific differences.

Some key questions arising from this work are as follows:

i) What is the best governance to manage interactions between stakeholders under an adaptive pathway?
ii) Are the interactions best managed through formal, informal, binding or non-binding agreements?
iii) How are conflict resolution and arbitration, best managed, and by whom?
iv) If disengagement from MAPPs occurs, how is this best communicated to all stakeholders in a transparent and timely manner?