



Seamless Process and Decision Points of an Adaptive Pathway

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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 D2.05 and D3.02 and only reflects the views of the authors.

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List of Abbreviations

- **AA** – Accelerated Assessment
- **ADAPT SMART** - Accelerated Development of Appropriate Patient Therapies: a Sustainable, Multi-stakeholder Approach from Research to Treatment-outcomes
- **ATMPs** – advanced therapy medicinal products
- **CMA** – Conditional Marketing Authorisation
- **CMC** – chemistry, manufacturing and control
- **CSA** - Coordination and Support Action
- **CT** – clinical trial
- **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
- **RCT** – randomised controlled trial
- **RWE** – real world evidence
- **SA** – scientific advice

Working Method

During advancement of the separate IMI ADAPT SMART deliverables of the D2.05 and D3.02 working groups, important intersections were recognised. In the work plan, D2.05 was charged with *“map(ping) out, within the current EU development/access pathways, the different transition/engagement moments¹ with stakeholders, and...(to) explore if these moments should be different for a MAPPs pathway”*. In turn, the D3.02 working group was responsible for *“contrast(ing) decision points in current vs. future processes by stakeholder groups and (identifying) implications for a roadmap for implementation”*. Therefore, over the preceding year, D2.05 and D3.02 have collaborated on a joint objective to delineate adaptive pathway process steps during development, authorisation and post-authorisation access along with the critical decision points for the involved stakeholders. There are many additional ADAPT SMART working groups with distinct objectives and deliverables with relevance to these D2.05/D3.02 objectives and vice versa where relevant reference is made to reports already completed. Hence, this document is merely process focused and should be read in conjunction with other ADAPT SMART deliverables; for example, it does not describe the principles of the MAPPs concept, engagement criteria for MAPPs products, workable ‘strategies’ for payers in case the product under-performs, or methodologies or data sources for generation of real world evidence (RWE).

Moreover, 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.

On 6 July 2016, the conceptual adaptive pathway model was presented and feedback received during a multi-stakeholder workshop in London, UK. From August through December 2016, participants of D2.05 and D3.02 – including representation across stakeholder disciplines – provided review and input on the conceptual adaptive pathway presented in this report.

¹ Within this report, ‘moments’ are considered as significant milestones during medicine development and post-authorisation patient access in which an assessment (or decision) is taken or multi-stakeholder engagement occurs.

Introduction

The development of a medicinal product from substance to a finished product, which can then be prescribed to patients, is a complex process involving many stakeholders. With the rapid evolution of science, society and technology, new medicine development must adapt to meet the growing scientific understanding of disease mechanisms but also meet the expectations of increasingly empowered patients. The emergence of genomics allows a more tailored development for each product based on a deeper understanding from the mechanism of action. Technology is also deeply modifying researchers capabilities to collect data and share information. There is a growing sense of urgency in this context from patients and physicians to access promising therapies as early as a positive benefit-risk balance is sufficiently established, though at a time where stakeholders will still have important questions to answer to establish the full therapeutic value of the medicine. An **adaptive pathway** can then be conceptualised as a development strategy that proactively considers a life-cycle approach with a focus on enabling early access for a limited patient population with a high unmet need. This customised development would benefit from the coordinated and repeated dialogue of the principal stakeholders. This development approach would also optimally use new data sources which are becoming increasingly available. In a similar way, EMA has defined ‘adaptive pathway’ as a “prospectively planned, adaptive approach to bringing medicines to market. The adaptive development plan will initially target the development to a well-defined group of patients that is likely to benefit most from the treatment. This is followed by iterative phases of evidence gathering and progressive licensing adaptations, concerning both the authorised indication and the potential further therapeutic uses of the medicine, to expand its use to a wider patient population as more data become available.”²

Therefore, we reflect that an adaptive pathway be viewed as a ***scientific and engagement conceptual framework*** (fully described in the following section along with Appendix 1) through which the stakeholders – collectively through **coordinated dialogue** when appropriate – provide input on the best path forward to a medicine developer for development and post-authorisation access, specifically for the particular medicine. In this way, this conceptual adaptive pathway represents an evolution from the typical process of more or less isolated stakeholder interactions, particularly for post-authorisation data collection (Appendix 2). It can be further conceptualised as a navigable pathway in which the developer engages stakeholders through coordinated dialogue to consider their distinct **toolkits**³ of approaches to

² http://www.ema.europa.eu/docs/en_GB/document_library/Report/2016/08/WC500211526.pdf [accessed Jan. 2017]

³ The analogy of the toolkit is intended to convey that, within an adaptive pathway, the stakeholders will specifically discuss tailored development and post-authorisation measures - may be processes, infrastructure, prerequisites or requirements - for each individual product. As such, some of these measures or tools (e.g., real world evidence, registries to monitor appropriate

optimally support development, authorisation and post-authorisation access processes. In this way, the medicine developer can institute an adaptive pathway to optimally coordinate and align the existing processes and involved stakeholders in a more integrated manner. For example, during development, regulators may offer the developer advice on the use of a number of regulatory tools such as (but not limited to); orphan designation, the PRiority MEdicine (PRIME) scheme, joint or parallel regulator/HTA scientific advice (SA) – currently, being used with more frequency – as well as accelerated assessment (AA) or conditional marketing authorisation (CMA). The objective is to identify the optimal strategy that will allow patients with high unmet needs to access a beneficial therapy at the earliest possible time point. An additional objective is prospective agreement on the evidence package and follow-up measures to answer the remaining questions relevant for the varied stakeholder to evaluate the long-term value of the medicine. Certainly, an adaptive pathway approach is not suitable for all medicines. More precisely, multi-stakeholder dialogue under an adaptive pathway approach is envisaged for those potential medicines that are consistent with the ADAPT SMART engagement criteria (e.g., address high unmet need with reasonable expectation of substantial added benefit for patients, and use of different data sources). These criteria are question based⁴:

1. Can we define a target population with a high unmet medical need? Does the product hold sufficient promise to address the unmet need?
2. Can a prospective iterative post-(initial) marketing authorization development plan be proposed, developed, implemented and agreed?
3. Are there workable tools to ensure appropriate product utilization?
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 interaction?
6. Which critical aspects for pharmaceutical development would need to be considered?

The tools of this conceptual framework are currently available. The intent of an adaptive pathway approach is to enable the developer to prospectively and collectively implement them by involving stakeholders to best navigate the course of the medicine’s lifespan. As such, the overall objective of an adaptive pathway is to agree the optimal strategy for the regulatory and HTA/payer evidence requirements to be met in the most efficient and effective way possible to facilitate development of and access to new medicines in high unmet need. In this way, an adaptive pathway as conceptualised in this report is not actually novel nor

patient usage) will likely be considered on a routine basis, while others (e.g., inclusion into the PRIME scheme, adaptive trial design) will likely be implemented on a case-by-case basis based on the particular circumstances.

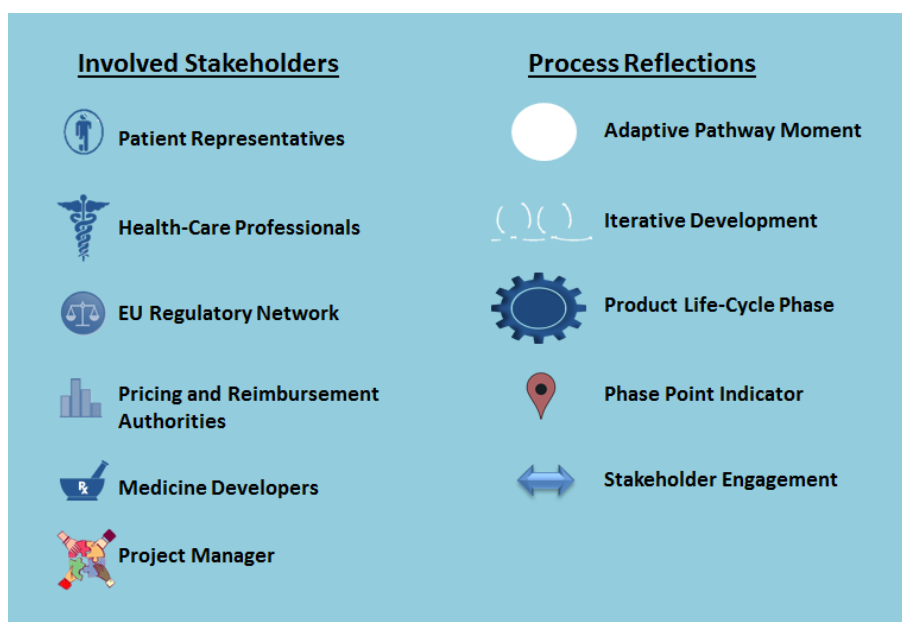
⁴ ADAPT SMART Discussion paper on Engagement Criteria for MAPPs from December 2016: <http://adaptsmart.eu> [accessed 24 January 2017]

an official designation – rather a deliberate method for facilitating and focusing collective multi-stakeholder engagement efforts across the development life-cycle.

Also, within this report, there is a pictographic representation of the proposed medicine development and access process steps or core ‘adaptive pathway moments’. This diagram visualises the conceptual engagement instances of significance in which involved and decision-making stakeholders share their respective views or take a decision, based on their remits, to continue progression of a potential medicine along a conceptual adaptive pathway to patients. These steps are described based on the existing EU regulatory and generalisable country access processes. As a result, this report identifies approaches and engagement moments enabling an adaptive pathway within these existing frameworks – i.e., ensuring that all existing tools are used in the most optimal way. Finally, this report does not aim to prescribe solutions or to assign roles and responsibilities. These deliberations will need to evolve with stakeholders in a next phase of ADAPT SMART. Therefore, the report lists a number of remaining questions in the concluding remarks.

Appendix 1 describes, in detail, the generated data, key events and involved stakeholders separated into each consequent phase of this adaptive pathway conceptual model. Under each graphic in this report, a table references the specific adjustments that will enable the adaptive pathway concept within the processes typically in use for the development and post-authorisation access of medicines in the EU. Finally, there is a narrative description of the essential changes to be considered within each stage. Deliberately, a simplistic model has been depicted to illustrate the potential decision and transition moments in the lifespan of a medicine. It is acknowledged upfront that implementation in practice will require further work. Considered in this way, the report provides a basis for continuing development of the framework allowing a dialogue amongst stakeholders about *what the conceptual model actually should include*, and correspondingly by default, *what it should not*.

Illustrative Symbols

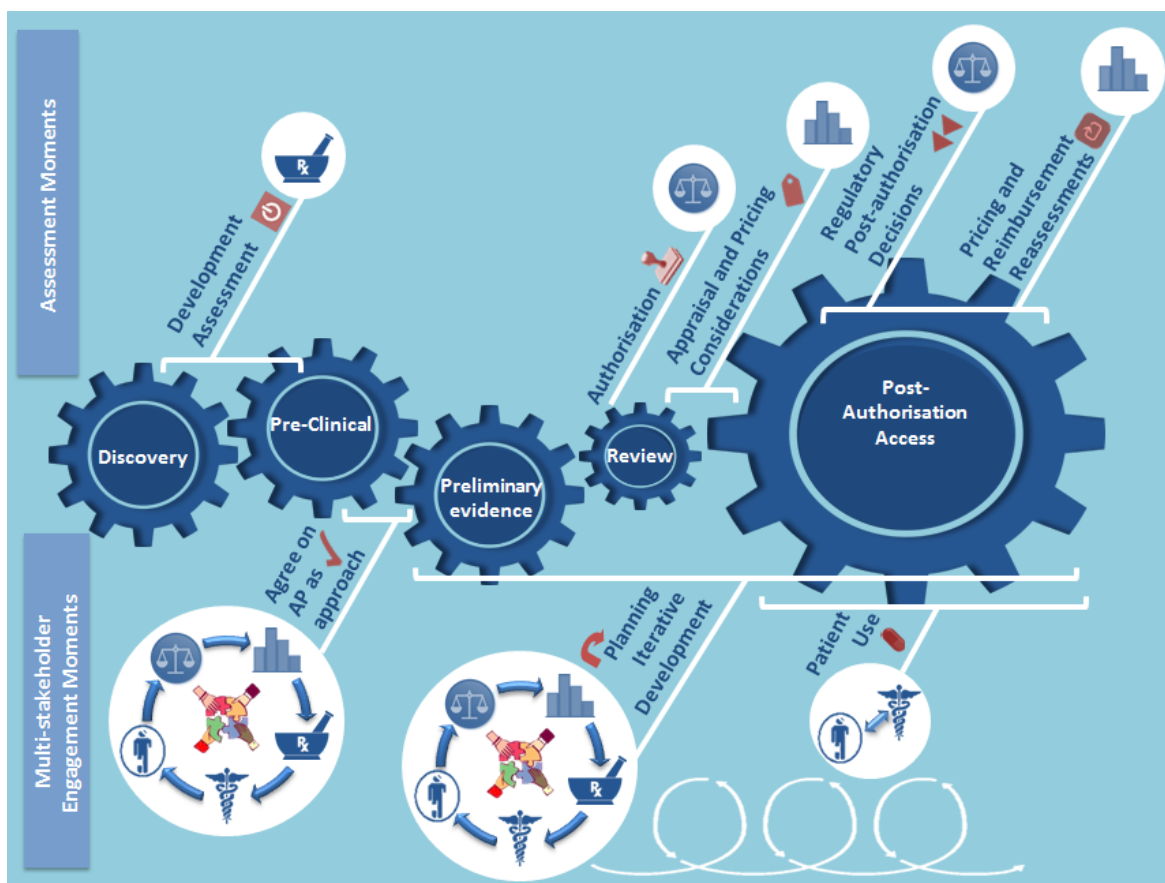





There are countless distinctions possible for the diverse range of stakeholder groups represented within this depiction, which are not possible to fully explore in this conceptual overview. For instance, countries are differently organised to decide on pricing and reimbursement. Not all have distinct HTA capabilities or assessors to inform payers' decision making. Different authorities in national healthcare systems will be in charge of evidence standards, healthcare priorities, price negotiations, budget management and reimbursement decisions.






- **Pricing and reimbursement authorities:** Throughout this report, HTA and payers will be collectively referenced as “pricing and reimbursement authorities”.
- **Health-care professionals:** Along with health-care professionals such as therapeutic experts and physicians, other experts such as ethicists, health economists, epidemiologists, and statisticians may also be consulted, though these experts are not directly represented here.
- **Patient representatives:** The stakeholder of “patient representatives” will not customarily be individual patients *per se*. In most instances, it is anticipated that a patient organisation(s) will represent patients' views. Although, for some rare diseases when a formal patient organisation is not established, patients and/or their caregivers may offer key insights through an adaptive pathway engagement process.
- **Process Reflections:** In this report, “process reflections” are represent key time points or periods within the adaptive pathway model.

Proposal for the core multistakeholder engagement and assessment moments enabling an adaptive pathway

Within the below diagram, each product life-cycle phase is symbolised by a blue cog. The separate cogs are comparatively sized to represent the characteristic duration of the phase during the lifespan of a typical medicine. The top half of the figure includes the assessment or decision moments by the stakeholder represented. Although these moments may be informed by multi-stakeholder inputs, in the end, the designated stakeholder makes an assessment and ultimate decision based on their respective remits. Within the bottom portion of the diagram, moments of multi-stakeholder engagement are illustrated.



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	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

		<p>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	Regulatory decisions are also taken during the post-authorisation phase. For example, regulatory decisions may lead to: <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.

The above model illustrates the core moments of an adaptive pathway and each is described in detail within this report. While these adaptive pathway moments are depicted two-dimensionally, of note, some of the engagement moments will likely occur in parallel and iteratively as the process progresses. The conceptual adaptive pathway approach is proposed within the current European and national legal frameworks. It is not the intention to suggest changes in these legal frameworks.


It is anticipated that the full implementation of the conceptual adaptive pathway approach may have significant advantages for each stakeholder. Foremost, therefore:

- Patients will experience benefits through the opportunity to provide organised input to new options for their medical needs and earlier access to these new medicines.
- Regulators have already mechanisms in place to facilitate adaptive pathway interactions, through multi-stakeholder scientific advice, and could make use of different regulatory instruments such as conditional marketing authorisation (CMA) and risk management plans.
- Health-care professionals or therapeutic experts will be able to contribute expectations about the medicine's use and positioning within the current management of the disease and assist in framing potential clinical value.

- Pricing and reimbursement authorities will have enhanced opportunities to provide early input on the data necessary to support their decisions, and gain a clearer understanding of the evidence package that will be available at time of initial regulatory approval. Pricing and reimbursement authorities will also be able to shape the post-authorisation evidence generation plan, anticipate indications and usage of the medicine that will be authorised, and gain earlier insights into horizon scanning and budgetary planning activities. The framework foresees an initial negotiation moment for payers as well as reassessment moments where the collected evidence is reviewed and pricing and reimbursement decisions potentially revisited based on the data.
- Medicine developers will obtain early, and continuous tailored, iterative input on the development plan to enhance the way in which development and post-authorisation evidence generation will transpire. Early interactions could expedite local pricing and reimbursement decisions and assist in determining suitable managed entry agreements (MEAs).

While these potential benefits are noteworthy, there are potential challenges such as stakeholder capability and resource implications that must likewise be considered, and are further mentioned within this report. The multi-stakeholder consultation will also provide greater visibility to the trade-off choices that stakeholders must consider. In sum, adaptive pathways will facilitate the utility of the generated data – both pre- and post-marketing authorisation (MA) – allowing stakeholders to make earlier, well-informed decisions with a mechanism to reevaluate these decisions as more information becomes available.

Development assessment

As an initial activity (i.e., represented by  in the figure), the medicine developer⁵ should assess the opportunity (e.g., severity of disease, characteristics of a potential medicine, regulatory therapeutic guidance and tools, pricing and reimbursement authorities' data interests) of each potential medicine, for example, seeking input from various stakeholders. This can already occur in practice, but for completeness this step is added in the conceptual framework since adaptive pathways places a special emphasis on high unmet need. It is not anticipated that this would be an interaction with each stakeholder at this development stage given the number of products that are evaluated during discovery and pre-clinical. Rather, the medicine developer may wish to informally seek input (e.g., from patient representatives and health-care professionals) and/or assess the evolving contextual environment in which they are

⁵ Medicine developer is modeled for illustrative purposes as a company; however, it could be a medicine developer from many other settings such as academia, advocacy organisation, etc. As such, some processes may be slightly modified depending on the nature or discipline of the developer.

operating (e.g., from the perspectives of regulators, pricing and reimbursement authorities) to better understand a therapeutic area or condition.

For example, the medicine developer will list patient organisations, evaluate registries or assess the most recent therapeutic area guidelines written by regulators, health care organisations and pricing and reimbursement authorities around the globe. In order to make an informed determination, the developer's decision should reflect early upon the unmet needs of patients and the broader healthcare ecosystem, as well the potential value proposition of the medicine. The medicine developer would typically consider a range of development approaches for each of its products, and portfolio tradeoff options across products even amongst those being developed for the same indication. At this early stage, the inputs primarily involve defining what the actual unmet patient need is to stimulate discovery and development. Along with the adaptive pathway engagement criteria, these assessments inform and influence early consideration of the potential value of using an adaptive pathway approach.

[Agree on adaptive pathway \(AP\) as optimal approach](#)

An adaptive pathway approach is only feasible if involved stakeholders agree that the medicine shows sufficient promise and – as a starting point for additional considerations - fulfills an unmet need. Considerations also include an assessment that the risks are likely proportionate, acceptable, and can be managed by the proposed strategy. For this purpose, ADAPT SMART proposed engagement criteria for an adaptive pathway (*see* Introduction). The essential element for this decision is the willingness of each stakeholder in contributing resources to provide meaningful advice to be considered in the evidence generation plan (✓). The process of reaching agreement on adaptive pathway engagement is not detailed as of yet. However, this adaptive pathway moment is expected to occur during either the pre-clinical or early clinical development stages. It is also clear that it will involve additional resources of each stakeholder and require the facilitation of a project manager. The roles and responsibilities of such a project manager as well as their affiliation need to be clarified further (*see* Concluding remarks and options for future work).

[Iterative development plan](#)

An “iterative development plan” is a development plan initiated by the developer, which integrates the feedback from the stakeholders and outlines the development of the medicine during its lifespan, including the phase after initial authorisation. Within this report *iterative development* is applied as a broad term also accounting for the generation of additional evidence and/or uncovering of new facts as time progresses. The iterative development plan extends over a significant period of time (and interactions) and supports an adaptive pathway approach from beginning to end. It is the vehicle for multi-stakeholder engagement at critical

development moments. Based on the data and input collected, the development plan will be regularly adjusted (↻).

It is envisaged that development planning discussions likely begin as informal, *safe harbour* interactions, and progress to more formal interactions such as joint or parallel EMA and HTA scientific advice (SA). The PRIME scheme offered by the EMA may be a good start to the process. Scientific advice and stakeholder discussions should occur in an early and iterative manner in order to inform the decision points along the product lifespan. Multi-stakeholder SA offer the platform for stakeholders to align on the evidence package required to demonstrate a positive benefit-risk profile and support regulatory authorisation. These interactions will also be used to consider the critical questions to be addressed, which warrant the discussion of plans for data collection pre- and post-authorisation. Scientific advice considers many aspects of product development and evidence generation such as biomarkers, surrogate and composite endpoints, subpopulations, chemistry, manufacturing and control (CMC) issues, adaptive trial design, patient reported outcomes (PROs) and key milestones to review post-authorisation evidence requirements.

For developers, scientific dialogue opportunities could assist in identifying the expectations of regulators and pricing and reimbursement authorities in terms of evidence requirements, which the developer can take into account when designing the medicine's clinical development plan. The early dialogue may also inform the developer's assumptions about the potential implications of the evidence requirements for subsequent national pricing, reimbursement, and funding conditions. Having all relevant stakeholders together to discuss tools, methods and sources of data may increase the mutual understanding of the challenges related to the generation of the required evidence, help inform potential tradeoffs, and ultimately increase the confidence in future study results.

In terms of data generation during preliminary evidence generation or clinical development, at a high level, this approach envisages the availability of iterative results (i.e., both 'early' and 'late' phase study results). Under an adaptive pathway, it is envisaged that clinical research will follow a more continuous design enabled by integrated stakeholder dialogue. As is possible today, the early dialogue might facilitate stakeholder agreement on the design of initial trials that focuses on high unmet need in more severe populations where shorter and/or smaller trials may allow for the detection of treatment effect. Also, discussed amongst the stakeholders is the potential integration of RWE as an adjunct to randomised CTs (RCTs). RWE and CTs in the post-authorisation setting may be considered to refine and confirm early benefit-risk assessments or the clinical effectiveness of the medicine after the initial authorisation. The same iterative development plan will support expansion (or contraction, if the new data is not sufficiently supportive) of the patient population and/or new indications.

However, the extent to which the use of RWE might be used in support of RCTs will be highly dependent on the nature of the product, endpoints used, methodologies, feasibility to collect quality evidence, and the current or proposed indication. The appropriate role of RWE within this adaptive pathways context will need to be determined on a case-by-case basis and plans will need to be tailored to the product in question. Other possible information and data changes under an adaptive pathway include: increased use of exploratory hypotheses built into adaptive trials, greater use of PROs, surrogate and bio-markers (e.g., co-development of drug and biomarker), and confirmatory studies continuing post-initial authorisation (e.g., pragmatic trials with inclusion criteria reflecting real-world practice and less-standardised treatment protocols).

During these iterative development planning moments, as evidence accumulates it is expected that the development strategy will be discussed, then the plan be adjusted and later reassessed, based on stakeholder dialogue and scientific advice. Notably, there is a need to identify the requisite competencies and expertise, and then to allocate and mobilise the required resources of stakeholders throughout the iterative development planning engagement. Leading up to initial marketing authorisation, the iterative development plan discussions may include a number of topics across disciplines though pertinent to the post-authorisation phase. In the peri-authorisation period there are stakeholder discussions and agreements regarding the post-authorisation approach such as risk management planning, measures for next milestone engagement moments (e.g., after a certain number of patients use the medicine or after a given time point). The evidence generation plan is discussed among the stakeholders and considers the critical questions to be addressed in order to also support subsequent pricing and reimbursement decisions at the national level. Further examples of discussion and agreement topics include, the collection of additional evidence through RWE (e.g., registries), post-authorisation safety studies (PASS), post-authorisation efficacy studies (PAES), and prospectively planned future indications. Managed entry agreements are discussed with national pricing and reimbursement authorities during pricing negotiations, though it is expected that they will draw on the evidence generation plan for their data needs. As the medicine is appropriately used by patients in the real world setting, stakeholders will confirm benefit-risk, assess appropriate utilisation, and/or demonstrate value.

Regulatory Authorisation

Authorisation (👉) is the decision by the regulatory authority to approve a medicine for patient use in a given therapeutic indication(s) based on the assessment of efficacy, safety and quality. Under an adaptive pathway approach, it is anticipated that authorisation may be conditional (i.e., CMA) or a full MA in a well defined population.

Appraisal and pricing considerations

The Member States have the sole responsibility for decisions with regard to reimbursement and pricing. The adaptive pathway moment of pricing and reimbursement authorities considerations (🔴) includes the assessment of the medicine's relative efficacy or effectiveness, the pricing negotiations and potential managed entry schemes/conditions. As pricing and reimbursement processes are different in each Member State, in this report, only high-level remarks will be offered regarding how an adaptive pathway approach could be implemented nationally.

The price of the medicine for the given indication(s) is determined by the local price and reimbursement authorities. As an option, MEAs are formal arrangements between a developer and a payer or healthcare provider that enables access to (coverage/reimbursement of) a health technology (such as a medicinal product) subject to specified conditions. These arrangements can use a variety of mechanisms to address uncertainty about the clinical benefit, utilisation or budget impact of the technology in clinical practice conditions. Under adaptive pathways, the medicine developer would engage in parallel SA involving regulators and HTA bodies to discuss a prospectively planned and integrated evidence generation plan addressing the regulatory requirements and to consider the critical questions from downstream pricing and reimbursement authorities.

The parallel SA discussions prior to the initial marketing authorization could facilitate better alignment of stakeholders around the evidence package expected to become available at the time of the initial regulatory authorisation as well as the evidence generation plan and resulting data expectations at set timelines post-authorisation. In principle, the initial evidence package would support both the regulatory authorisation (i.e., provide evidence of a positive benefit-risk profile) and enable the initial price and reimbursement negotiations and design of suitable MEAs (or alternative pricing and reimbursement approaches) across the different national jurisdictions. Typically, payment models would have to be aligned with national processes and be tailored to the product in question and or preferences of payers and developers. Under this conceptual adaptive pathway model, local HTA recommendations and reimbursement decisions will hopefully rapidly follow the regulatory decision since HTAs and some payers (as represented by “pricing and reimbursement authorities” in this model) would have been involved in these early and iterative SA moments.

The evidence accumulated post-authorisation would be re-assessed by the relevant stakeholders according to pre-set timelines and may in some instances and geographies lead to a renegotiation of the initial price and or reimbursement conditions. The terms of the MEAs

may specify the consequences on price and reimbursement conditions of successful and unsuccessful confirmation of the value proposition. In this context, an adaptive pathway approach may require an adaptive pricing approach with price and conditions negotiated on a per country basis and revisited at set milestones in light of the results of the evidence available post-authorisation.

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 within the indication(s) of the marketing authorisation as early as a positive benefit-risk is established (🔴). The engagement criteria for adaptive pathways underscores the need for sufficient assurance that the medicine will reach the right patient and only the right patient. (Note that these considerations are also important factors for non-adaptive pathway medicines.) If this is not feasible, an adaptive pathway approach might not be the best solution for a particular medicine. Under an adaptive pathway, the topics for which it is necessary to inform patients about using a medicine should be discussed including by the ‘patient’ stakeholders through the adaptive pathway engagement moments.

Promotion of off-label use will be controlled and access to product used on-label can be further restricted by reimbursement criteria at the national level. However, in most Member States, health-care providers have the freedom to prescribe for the patient benefit a medicine outside of its approved indication(s). (Note that in some Member States this may require regulatory authorization.) In case of authorisation under an adaptive pathway, tools should be considered to optimise the appropriate use. For example, in addition to the SmPC, the black triangle indicating additional monitoring, the risk management plan and the follow up measures contained in the iterative development plan (e.g., ongoing CTs), therapeutic guidelines or restricted access through a center of excellence should be considered with health practitioners. The measures will depend, in part, upon national laws and can be discussed with national authorities during the access negotiations. The suite of options should be considered under early stakeholder discussions. Finally, consideration of early patient access (e.g., compassionate use) may occur on a case-by-case basis accounting for national laws and systems and the quality of the data package.

Consideration to widen the indication(s)

This proposed adaptive pathway foresees the possibility of an initial MA in a well-defined patient subgroup and subsequent confirmation or widening of the indication to include

additional indications in a larger patient population based on additional evidence gathered (e.g., RCTs, RWE) and/or a CMA where initial data are supported or confirmed through the collection of post-MA data on the product's use or additional CTs.

Regulatory post-authorisation decisions and pricing and reimbursement reassessments

These represent a commitment towards stakeholders to provide more data, a need for justification in case the developer neglects to follow up, and a way to enact consequences if the data are not generated or do not confirm the early assumptions. The multi-stakeholder dialogue during the iterative development plan offers the opportunity to discuss upfront expectations and some of the development and feasibility challenges that might emerge.

The post-authorisation access adaptive pathway moments of regulatory decisions and pricing and reimbursement reassessments (represented as ◀ and 📅, respectively) occur as per the conditions agreed upon at initial assessment and compiled in the evidence generation plan. These are the moments planned by stakeholders to review the commitments and data agreed upon in the iterative development plan. These decisions are taken and reassessments are conducted separately by the various stakeholders. However, stakeholders, including developers, should inform each other about decisions taken, as these may have consequences for the other stakeholders involved. Note that the nature of these interactions needs further deliberation and clarification.

Importantly, as in the pre-authorisation adaptive interaction moments, during decision and reassessment moments, each stakeholder maintains their well-defined remit and responsibilities:

- Regulatory authorities monitor the fulfillment of obligations and review respective data generation (e.g. as part of a CMA) with the possibility subsequently to take regulatory action (e.g. variation or withdrawal), and conduct regular reviews of the benefit-risk balance based on an assessment of any other collected post-MA evidence.
- Health-care professionals and patient representatives may be involved in adjusting therapeutic area practice guidelines to accommodate new information obtained.
- Pricing and reimbursement authorities may conduct a review of the optimal usage of a medicine based on assembled RWE. Pricing and reimbursement reassessments will occur at predefined time points and may trigger potential adjustments of price or reimbursement conditions at the national level.

It is foreseen, in this conceptual framework, that in some instances the post-authorisation data may not fully support the initial indication or patient population. In these situations,

stakeholders would take efforts to collaborate quickly with an appropriate reaction to ensure patients' best interests. As a consequence, it may be necessary to discontinue or modify early access (i.e., patient usage, contract) as per the post-authorisation data for this particular indication.

Note on Traditional Sequential Model of Interaction

The possibility exists for a product which was once progressing under an adaptive pathway to no longer meet the engagement criteria, and therefore, lose the benefits (see examples of anticipated 'benefits' introduced under the "Proposal for the core multistakeholder engagement and assessment moments" section above) of this approach. This will apply when an adaptive pathway approach ceases to add value and stakeholders decide to stop using this route to support the pre- or post-authorisation development of a specific medicine. An adaptive pathway approach has been conceptualised here as a scientific framework using existing tools and standards and assisting in their holistic implementation through the prospective engagement of stakeholders. Exiting this coordinated engagement approach will primarily affect any additional support offered through multi-stakeholder consultations and the emphasis on early access, though the tools and standards will still be available, as applicable, to the medicine developer, outside of an adaptive pathway approach. The mechanism of ceasing an adaptive pathways approach requires further careful deliberations to take into account the various constituent stakeholders' considerations.

Concluding remarks and options for future work

This report proposes a framework with pictographic representation of an adaptive pathway containing key moments, events and involved stakeholders, in each phase. This model is purposefully presented rather simplistically in this first evolution, acknowledging that there remain several questions to be answered – both unique to each individual potential medicine as well as to full implementation of an integrated adaptive pathway approach.

Some key questions (amongst others) arising from this work are as follows:

- i) How can Member States that do not have pricing and reimbursement authority resources effectively contribute to early input within this framework?
- ii) How will stakeholder resourcing be planned, managed, measured and assessed (in terms of impact)?
- iii) To what extent, and how, are formal interactions between stakeholders governed under an adaptive pathway?
- iv) How best should the process ensure the necessary patient inputs?
- v) How can a single iterative evidence development plan be maintained while supporting Member State-specific post-authorisation processes regulated by national laws?
- vi) What is the nature, remit, and stakeholder affiliation of a project manager for an adaptive pathway from start to finish? Where does potential project management expertise and resources currently reside?

The success of adaptive pathways, at least initially, may hinge on demonstrating true value via ‘live assets’ going through the pathway and integrating those key learnings moving forward. Greater shared experiences of pricing and reimbursement authority evidence requirements across Member States, coupled with their early consideration within an adaptive pathway (on a product specific basis) would be a vital enabler for the development, pricing and reimbursement processes, and reassessment decisions, of a successful adaptive pathway product development.

The nature of the early informal, and later formal multi-stakeholder interactions, will require a delicate balance between maintaining appropriate levels of transparency versus confidentiality, being respectful to the political mandate of each stakeholder’s involvement, and ensuring mutual trust that each stakeholder is, and remains committed to, the decisions and processes they have agreed. The development and implementation of such a mechanism requires careful consideration.

Appendix 1: More Detailed Description of each Adaptive Pathway Phase

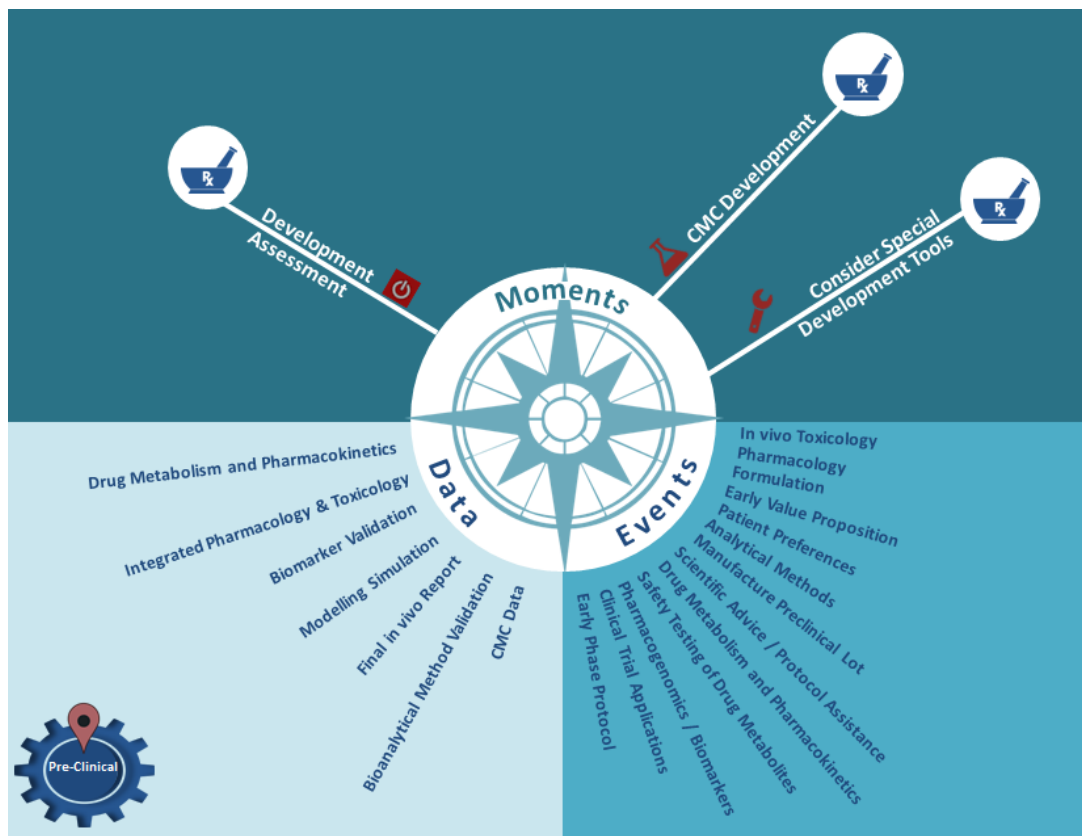
In Appendix 1, the distinct phases or disciplines of medicine development, authorisation and post-authorisation access are reviewed in greater detail. This section of the report is intended to highlight additional technical aspects of an adaptive pathway as supportive information to the core adaptive pathway moments previously outlined. Over time, further process and decision step details could be amplified by ADAPt SMART using Appendix 1 as the conceptual framework. Key components of the adaptive pathway conceptual model involve:




- (i) an evolution from the traditional sequential approach with limited concerted multi-stakeholder interactions, involving adaptive and overlapping processes;
- (ii) use of the same tools but in a different order in many cases; and
- (iii) an emphasis on early multi-stakeholder interactions, – with predominantly prospective planning and strategising.

Several years ago, the concept was given the title of Medicines Addaptive Pathways to Patients, abbreviated as MAPPs. Fittingly, as described in this concept for a seamless pathway through adaptive interactions of stakeholders, an individual product would take a discrete path through the integrated phases of an adaptive pathway approach. Consequently, one can further correlate “MAPPs” to a ‘*map*’ by which the course of an actual medicine’s life-cycle is charted through the involvement of engaged stakeholders. Within the subsequent diagrams, a ‘*compass*’ (represented below) offers an orientation to the full complement of proposed adaptive pathway moments, significant events and generated data necessary to navigate the passage for a new medicine. These figures illustrate the additional adaptive pathway moments beyond the essential milestones described earlier in this report. Some of the moments, events and data may occur over a range of time points or across a number of phases and may not be a singular activity. For reference and contrast, the traditional development approach, including the key processes and tools, is included in Appendix 2.




Pre-clinical Adaptive Pathway Moments




	Adaptive Pathway Moments	Description of the Process Steps and Decision Points
	Development assessment	As previously described in core adaptive pathway moments.
	CMC development	Some modifications to the traditional CMC development paradigm are foreseen and should be considered early for a product that may fit the adaptive pathway engagement criteria.
	Consideration of special development tools	The medicine developer should give initial consideration of the special development and/or regulatory designations and tools (e.g., PRIME) to determine if any are applicable for a particular potential medicine.

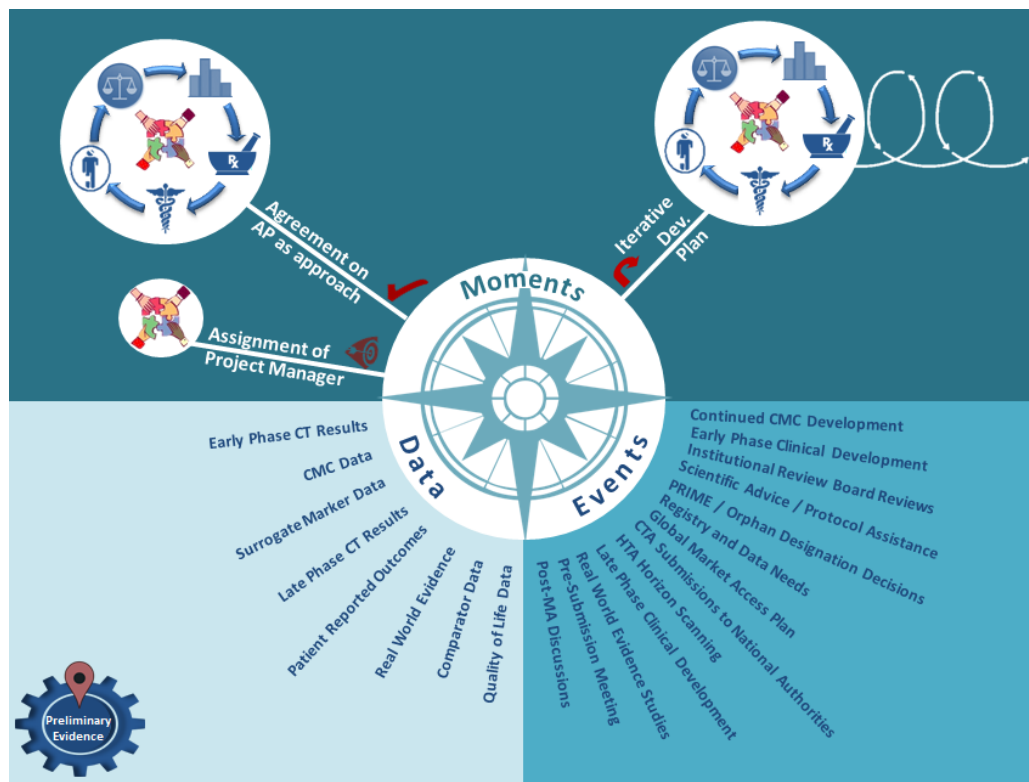
CMC Development




During the pre-clinical phase, much of the activities are commenced by the medicine developer. Chemistry, manufacturing and control (CMC) development considerations may need to be initiated earlier for potential products in order to enter an adaptive pathway. In the diagram, the CMC development () adaptive pathway moment reflects that some modifications to the traditional paradigm are foreseen and should be considered early for a product that may fit the adaptive pathway criteria. By itself, CMC development is a complex series of activities rather than a single moment. CMC may take a prominent – and rate-limiting role – especially for advanced therapy medicinal products (ATMPs) which may require the start of stakeholder engagement even earlier than for conventional products.

Consideration of special development tools


The symbol  represents the general period of time during development in which a developer should initiate discussions about the potential applicability of the special EU designations, development and regulatory tools – i.e., reflection on using the various tools. For example, among other tools, conditional marketing authorisation (CMA), orphan designation, PRIME scheme, multi-stakeholder scientific advice (regulatory and HTAs). Early consideration of the use of some of these tools including novel development tools could help inform clinical trial protocols. An initial, informed strategy will also help the medicine developer in preparations for the multi-stakeholder adaptive pathway engagement moments that follow.

Preliminary Evidence Adaptive Pathway Moments

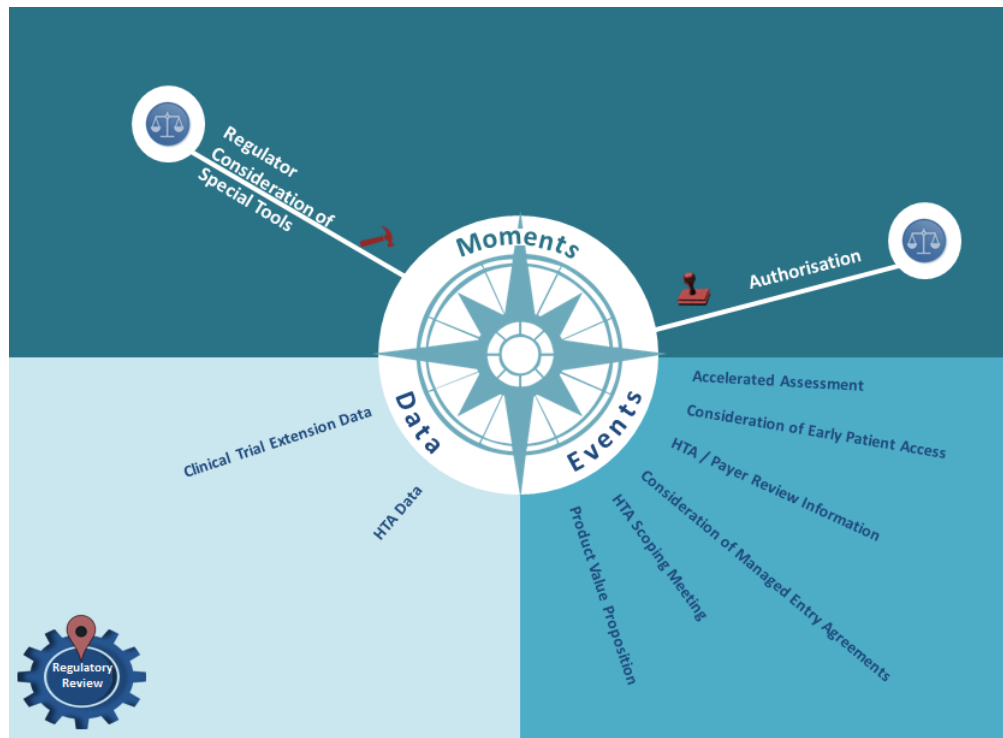




	Adaptive Pathway Moments	Description of the Process Steps and Decision Points
	Assignment of project manager	A project management resource coordinates the multi-stakeholder decision on commitment to an adaptive pathway and the iterative development planning.
	Agreement on MAPPs engagement	As previously described in adaptive pathway moments.
	Adaptive development plan	As previously described in adaptive pathway moments.

Assignment of project manager


The preliminary evidence phase of the proposed adaptive pathway introduces a number of instrumental process modifications compared to typical development approaches – all intended to enhance the stakeholder interactions in order to gain insights on the relevance of data generation and facilitate timely patient access. Through an appreciation of the complexities of logistical coordination, nuanced remits and responsibilities, and differing processes of the stakeholders, a project manager (referenced as PM in the paper and  in the diagram) is necessary to coordinate the logistics and manage the enhanced, iterative engagement moments. The PM should serve as a consistent point of contact for all stakeholders who will provide input into the iterative development plan. The detailed roles and responsibilities of the PM need to be further explored (see Concluding remarks and options for future work).

Regulatory Review Adaptive Pathway Moments

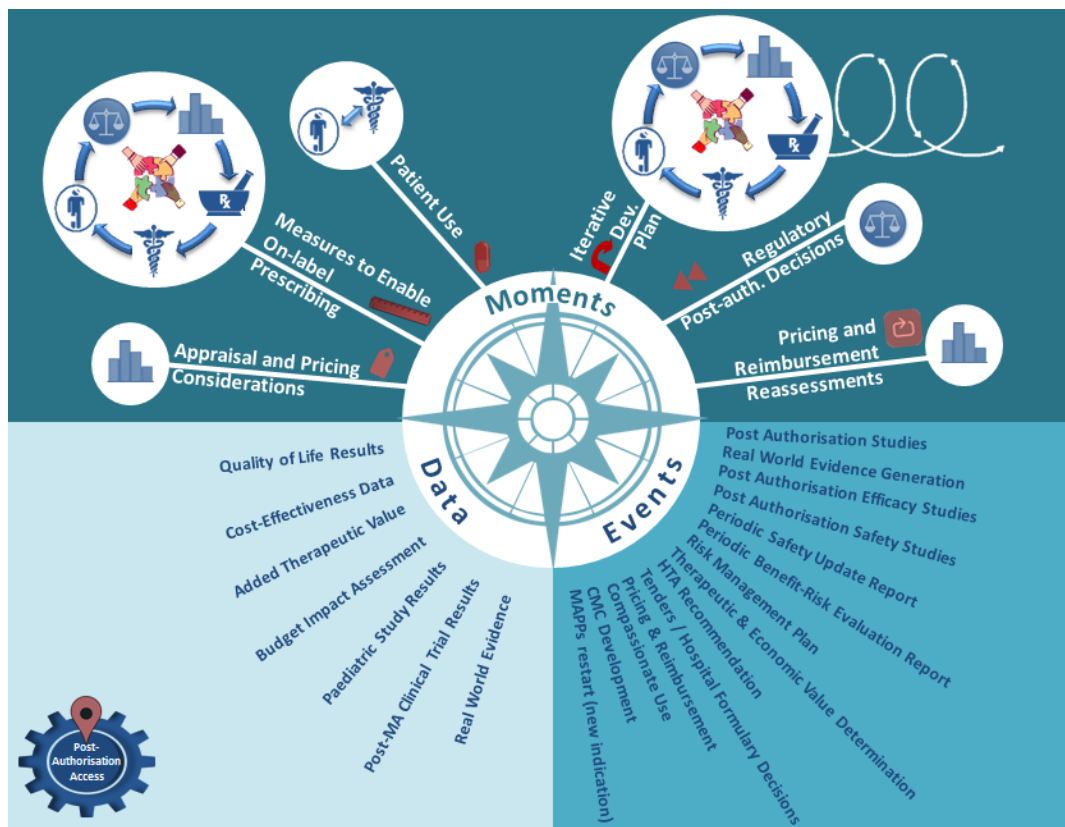


	Adaptive Pathway Moments	Description of the Process Steps and Decision Points
	Regulator consideration of special tools	It should be possible to identify applicable, early candidates for CMA and AA.
	Regulatory authorisation	As previously described in adaptive pathway moments.

Regulator consideration of special tools

Well before the marketing authorisation application (MAA) is submitted, and following the prospective proposal by the medicine developer, final considerations should be given to the applicability of special regulatory authorisation tools such as CMA and accelerated assessment or AA (). These actions will continue the considerations during iterative development planning to early prepare for post-authorisation data collection activities.


Post-Authorisation Access Adaptive Pathway Moments




	Adaptive Pathway Moments	Description of the Process Steps and Decision Points
	Appraisal and pricing considerations	As previously described in adaptive pathway moments.
	Measures to enable on-label prescribing	Considerations and tools to enable the prescription in the desired population to be acceptably consistent with the authorised therapeutic indication(s).
	Patient use	As previously described in adaptive pathway moments.
	Iterative development plan	An iterative development plan in the post-authorisation setting refers to an evolving product development strategy, following an initial MA decision.
	Consideration to widen the indication(s)	Cases of an initial MA and reimbursement of a medicinal product within a well-defined patient subgroup and a subsequent widening of the indication to a larger patient population
	Regulatory post-authorisation decisions	As previously described in adaptive pathway moments.
	Pricing and reimbursement reassessments	As previously described in adaptive pathway moments.

Measures to enable on-label prescribing

Particularly applicable to the early post-authorisation timeframe, this adaptive pathway moment represents the multi-stakeholder discussions and agreement on tools to enable prescription in the desired population with usage to be acceptably consistent with the authorised therapeutic indication(s). There are measures available to multiple stakeholders to

help facilitate this activity. For example, depending on the jurisdiction, approaches of payers and guideline developers could be harnessed (see section on Patient Use) ().

Iterative development plan (post-authorisation)

An iterative development plan after marketing authorisation reflects the evolving product development strategy, which is agile in accommodating the views of the stakeholders () gained through multi-stakeholder interactions. Planning for post-MA development is always initiated in the pre-authorisation phase and will include considerations on the merit of real world evidence (RWE) collection and analysis, and adaptive trial designs to answer the relevant questions, but continues post-MA and can be viewed as a cohesive, singular plan as previously mentioned. As the medicine is used by patients in the real world setting, stakeholders continue dialogue on additional evidentiary needs to confirm benefit-risk, assess appropriate utilization, and/or demonstrate value. Likewise, the post-MA development plan iteration moments should continue to be organised by a project manager. These aspects are purposely presented and discussed at a general, conceptual level within this paper.

Appendix 2: Traditional Sequential Development and Post-Authorisation Access

This diagram depicts a collated and high level summary of the key R&D and patient access phases, and key events and interactions with key stakeholders, as they typically transpire today. This provides a useful comparative reference to the proposed conceptual adaptive pathway approach.

