

ADAPT-SMART

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

PROJECT OVERVIEW

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LIST OF ABBREVIATIONS

ADAPT-SMART	Accelerated Development of Appropriate Patient Therapies: a Sustainable, Multi-stakeholder Approach from Research to Treatment-outcomes
ATMP	Advanced Therapy Medicinal Products
CASMI	Centre for the Advancement of Sustainable Medical Innovation
CMC	Chemistry, Manufacturing and Controls
CSA	Coordination and Support Action
DG GROW	Directorate General for Internal Market, Industry, Entrepreneurship and SMEs
DG SANTE	Directorate General for Health and Food Safety
EAMS	Early Access to Medicines Scheme
EBE	European Biopharmaceutical Enterprises
ESIP	European Social Insurance Platform
EU	European Union
EUnetHTA	European network for Health Technology Assessment
FDA	US Food and Drug Administration
FP7	Seventh Framework Programme for Research and Technological Development
HCPWP	European Medicines Agency's Healthcare Professionals' Working Party
HTA	Health Technology Assessment
IMI	Innovative Medicines Initiative
IT	Information Technology
JU	Joint Undertaking
M&S	Modelling and Simulation
MAPPs	Medicines Adaptive Pathways to Patients
MEDEV	Medicine Evaluation Committee
NEWDIGS	NEW Drug Development ParadIGmS
O2 problem	Opportunities and Obstacles
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
R&D	Research and Development
RCT	Randomised Controlled Trials
SME	Small and Medium sized Enterprise
SmPC	Summary of Product Characteristics
SOFIA	Submission OF Information Application
STAMP	Safe and Timely Access of Medicines for Patients
TBD	To be decided
US	United States
WP	Work Package

LIST OF PARTICIPANTS

Participant	Organisation name	Country
1. TI PHARMA	Stichting Top Institute Pharma (Escher Platform)	The Netherlands
2. DHMA	Danish Health and Medicines Authority (representing EUnetHTA and DHMA)	Denmark
3. EPF	European Patients' Forum	Belgium
4. MIT	Massachusetts Institute of Technology's NEW Drug Development ParadIGmS (NEWDIGS)	United States of America
5. EMA	European Medicines Agency	United Kingdom
6. UOXF	The Masters and Scholars of the University of Oxford (CASMI)	United Kingdom
7. EURORDIS	European Organisation for Rare Diseases	France
8. NICE	The National Institute for Health and Care Excellence	United Kingdom
9. HAS	Haute Autorité de Santé	France
10. ZIN	Zorginstituut Nederland	The Netherlands
11. BMS	Bristol-Myers Squibb	United States of America
12. ABBVIE	AbbVie	United Kingdom
13. AMGEN	Amgen	Belgium
14. ASTELLAS	Astellas	United Kingdom
15. AZ	AstraZeneca	Sweden
16. BSP	Bayer AG	Germany
17. BI	Boehringer Ingelheim	Germany
18. GSK	GlaxoSmithKline	United Kingdom
19. IPSEN	Ipsen	France
20. JPNV	Janssen Pharmaceutical Companies	Belgium
21. ELI LILLY	Eli Lilly and Company	United Kingdom
22. HLU	H. Lundbeck A/S	Denmark
23. LYSOGENE	Lysogene	France
24. MERCK	Merck KgaA	Germany
25. MSD	Merck Sharp & Dohme	United States of America
26. NOV	Novartis Pharma AG	Switzerland
27. NOVO	Novo Nordisk	Denmark
28. PFIZER	Pfizer, Inc.	United Kingdom
29. ROCHE	F. Hoffmann-La Roche AG	Switzerland
30. SARD	Sanofi S.A. / Genzyme Sanofi	France
31. UCB	UCB	Belgium
32. EFPIA	European Federation of Pharmaceutical Industries and Associations	Belgium

1. EXCELLENCE

1.1 Objectives

The overall scope of ADAPT-SMART is to establish an enabling platform for the coordination of Medicines Adaptive Pathways to Patients (MAPPs) related activities within IMI 2 and engaging a dialogue with relevant stakeholders. MAPPs seeks to foster access to beneficial treatments¹ for the right patient groups at the earliest appropriate time in the product life-span in a sustainable fashion. The ADAPT-SMART consortium will facilitate and accelerate the availability of MAPPs. This is enabled by the overall objectives of ADAPT-SMART, which are to:

- Identify relevant MAPPs activities, synthesizing the learnings from ongoing or completed pilots and case studies, creating a MAPPs repository of knowledge and opportunities;
- Identify the scientific challenges and opportunities related to MAPPs implementation and facilitate aligned understanding of consortium members and their constituents;
- Support new IMI 2 research and innovation actions by facilitating the inclusion of MAPPs enablers (tools and methodologies) to address/exploit the identified challenges and opportunities;
- Conduct horizon scanning and gap analysis for each topic identified, for methods, tools, and other relevant activities and producing actionable advice and/or recommendations for future research activities to IMI and other stakeholders to further the implementation of MAPPs.

1.2 Relation to the call topic text

This project overview relates to Call “IMI2-2015-04-01: Enabling platform on medicines adaptive pathways to patients” – Coordination and Support Action (CSA).

In line with the overall scope of this CSA, the ADAPT-SMART consortium will contribute its experience with MAPPs from several angles and its significant convening power to establish an enabling platform with relevant stakeholders for (i) the coordination of MAPPs related activities within IMI2 and (ii) engaging a dialogue with these stakeholders.

The project overview is based on a holistic approach, addressing all aspects of MAPPs and considering all relevant stakeholder perspectives to address the challenges identified in the call topic.

The ADAPT-SMART consortium is made up of a selection of major stakeholders involved in many of the initiatives specifically mentioned in the call text, such as the EMA Adaptive Licensing Pilot project, NEWDIGS, the UK's Early Access to Medicines Scheme (EAMS), and related IMI projects such as IMiPACT and GetReal. All consortium members have networks that collectively reach all relevant stakeholders.

1.3 Concept and approach, quality of the coordination and support measures

Progress in the life sciences and related technologies offers the potential to bring a wide range of beneficial therapies to patients over the coming years. There will be more personalised or stratified medicines, combinations, borderline products, and advanced therapies that will require new ways of evaluation and new ways of managing utilisation in clinical practice.

The current paradigms of bringing innovation to patients are also challenged by transformative environmental developments:

- Growing patient demand for timely access to promising therapies, exacerbating the ‘access versus evidence conundrum’. In turn, this will require more flexibility and increased numbers of iterations of regulatory and reimbursement decisions;
- Increased fragmentation of treatment populations due to better disease stratification, challenging the established clinical development pathways, e.g. large conventional phase III studies;
- Rising payer influence on product accessibility and growing concerns over budget impact of new treatments; financial pressures on health systems and sustainability challenges are raising questions

¹ Beneficial in this context is used in terms of anticipated value added for patients (addressing medical needs), healthcare and social security systems overall (health outcomes), it is not used in a, narrower, economic meaning.

regarding prioritisation of investment and value of innovation.

- Pressure on pharma/investors to ensure sustainability of drug development as pharmaceutical R&D attrition rates remain high and the cost of biopharmaceutical R&D continues to rise; this limits the absolute number of candidate drugs that can be brought forward.

To address these environmental changes while fully realizing the potential of scientific progress for patients in a timely and sustainable way will require major adaptations to current paradigms. The changes required go far beyond the well-defined remit of regulatory evidence standards. We posit that all decision makers and stakeholders in the healthcare ecosystem will need to explore a life-span approach to new pharmaceutical treatments with drug development, licensing, reimbursement, use in clinical practice and monitoring viewed as a continuum. The life-span approach is hereafter referred to as Medicines Adaptive Pathways to Patients (MAPPs). Detailed definition of the MAPPs concept, its key features, potential merits and weaknesses have been described elsewhere (ref. 1-4).

Strong public health drivers, enabling technologies, and our own collective experience convince us that there are sufficient opportunities for making the MAPPs approach a reality - now. There is, however, the “O2 problem” with MAPPs that is defined by the related Opportunities and Obstacles. A major task for ADAPT-SMART is the identification of these two Os, and to provide a framework for MAPPs that will overcome the latter and seize the former.

At present, we see the following key **opportunities**:

- The research-based industry’s pipelines are filling up: a number of innovative therapies are at advanced stage of development;
- Next Generation Sequencing, capture of phenotypic and behavioural data (digital biomarkers), and other predictive markers enable increasingly precise definition of the “right patient”;
- In turn, this is expected to result in better effect sizes, improved individual benefit-risk, and lower numbers-needed-to-treat with higher value in a given treatment-eligible population;
- Progress in advanced therapies (e.g. gene therapies) will make possible one-time curative interventions;
- Innovative clinical trial designs allow for more efficient and seamless knowledge generation;
- Improved understanding of disease processes (e.g. background rates of disease progression), and better knowledge management combined with modelling and simulation (M&S) increase the efficiency of knowledge generation, within randomised controlled trials (RCTs) and observational studies;
- Rapid learning systems in the healthcare environment enable improved knowledge generation post initial licensing;
- In turn, this allows decision makers to migrate from prediction to monitoring, supporting the MAPPs concept;
- More active contributions from patients/patient organisations provide opportunities for better definition of patient preferences and acceptable uncertainty about benefits, harms, and value of new products at the time of launch;
- Availability of increasingly effective tools to steward appropriate, targeted prescribing (in some healthcare environments);
- Cultural change with multi-stakeholder platforms already established, with more opportunities for data and information sharing across regions and groups.

At the same time, we recognise that important obstacles need to be addressed if MAPPs is to become a reality. At present, we identify the following key **obstacles**:

- The MAPPs concept, involving earlier access for (some) patients with more limited data will not be acceptable for some stakeholders; perception that (too) early launch could lead to serious safety problems and undermine public trust in the system;
- More drugs for more, but smaller, patient subpopulations (with differing levels of evidence) will make it difficult to achieve sustainability for both the research enterprise and healthcare payers; debates over price and budget-impact will become ever more contentious, willingness of payers to accept the MAPPs

concept with early access and initially limited data is likely to be poor;

- In some cases, limited data exclusivity duration after the initial (narrow) license may be a disincentive to drug developers;
- There is a risk that the concept of MAPPs will find uneven acceptance across EU member states; this may in part be a result of existing diversity of patient access across the EU (e.g. Eastern versus Western EU member states).
- The political will and legal tools to limit access to an approved drug to a subset of the population, as foreseen by MAPPs, may not be in place in some healthcare environments; avoidance of off-label use after an initial authorisation may be challenging;
- It may be politically difficult to remove a drug from the market or restrict payment should the initial benefit risk balance or value proposition not be confirmed post approval;
- MAPPs concept may present specific challenge for orphan drugs in light of the terms of EU orphan legislation (e.g. the concept ‘significant benefit’ which is unique to orphan designations);
- Resistance to flexible or outcome based reimbursement strategies due to practicalities and costs associated with implementing them;
- Perception that MAPPs concept entails a shift from evidence generation by way of RCTs to observational studies which have lower evidence standard;
- MAPPs will cause extra work load/new expertise requirements for regulators, HTA bodies, and payers, in light of repeat cycles of assessment and negotiations with sponsors (may lead to resistance to change);
- Legal, healthcare systems, and other differences across jurisdictions may challenge global evolution towards MAPPs principles (given global nature of firms and diseases);
- Need for capacity building and support for all stakeholders in order to fully integrate the contribution of patients and patient organisations across the R&D cycle.

Currently, several initiatives are exploring new pathways to market. These initiatives include the EMA Adaptive Licensing Pilot project, the New Drug Development Paradigms (NEWDIGS) initiative at Massachusetts Institute of Technology (MIT, USA), and the UK's Early Access to Medicines Scheme (EAMS). Parties directly involved with these initiatives, related IMI projects such as IMiPACT and GetReal, and several EU national developments, are joining forces in ADAPT-SMART with the aim of defining and helping to implement the MAPPs concept.

ADAPT-SMART is thus aligning a limited number of major stakeholders eager to progress towards MAPPs implementation. The consortium will mobilise its network of additional relevant stakeholders to adequately involve all players in the innovation life span. The ADAPT-SMART Coordination and Support Action (CSA), will act as a neutral collaborative framework to establish the platform that will engage with all relevant stakeholders, including patients, industry, SMEs (Small and Medium sized Enterprises), regulators, Health Technology Assessment bodies (HTAs), payers (national and European Networks), clinicians, governments/policy makers (national authorities as well as European Commission's DG SANTE and DG GROW, and European Networks).

In addition to engaging in a dialogue with relevant stakeholders, the ADAPT-SMART consortium will contribute to align understanding of the impact of MAPPs, to share learnings between all stakeholders, and to allow the field to actively work towards MAPPs implementation. This will increase the probability of successful innovation and accelerate access to crucial therapies, thus improving the position of both the patients in need of novel treatments and the research-based pharmaceutical industry.

This project overview entails the outlines for the conceptual approach for the establishment of a dedicated forum to enable (i) gap analysis, to identify scientific challenges and opportunities for the application of MAPPs. For example, EMA will bring in all learnings of its Adaptive Licensing Pilot project (which includes learnings through other stakeholders), and account will be taken of tools, methodologies and infrastructures developed in IMI projects and other initiatives (including those mentioned above), (ii) informing research activities, to facilitate the inclusion of MAPPs enablers (tools and methodologies) in new IMI2 and other research and innovation actions based on the gap analysis, and (iii) knowledge management, i.e. horizon scanning on non-IMI activities relevant to MAPPs to

create a comprehensive repository of knowledge and opportunities for coordination. These activities are described in more detail in Section 3 of this overview.

The CSA activities will be structured to systematically address all relevant subjects related to the three overarching work package themes of ADAPT-SMART:

1. Evidence generation throughout the life cycle;
2. Designing the MAPPs pathway;
3. Decision-making, sustainability & implications.

The ADAPT-SMART activities include the organisation of specific meetings along defined work package themes. In addition, attention is being paid to the involvement of all stakeholders, also beyond these meetings; wide-spread dissemination/communication of all ADAP-SMART conclusions and recommendations is ensured. To mobilise the necessary expertise and to engage the relevant stakeholders, the following is taken into consideration in the work plan described in Section 3, in particular in the project management activities in Work Package (WP) 4:

- Alignment of interests and mind-sets of the various stakeholders and decision makers along the entire value chain will be key to making MAPPs a viable route to market where appropriate in the future.
- Enabling discussion among stakeholders with non-aligned interests that need to be respected and balanced against each other.
- Ensuring that non-EU perspectives are taken into account to the extent possible, with a view to supporting global pharmaceutical R&D pathways.
- Ensuring that all relevant parties are involved in shaping the MAPPs concept. This may necessitate inviting experts from additional stakeholders during the course of the CSA (most likely in the Stakeholders Network, see Section 3.2).
- Provide scientific input for the ongoing work of the European Commission Expert Group on 'Safe and Timely Access of Medicines for Patients'-STAMP (Member States' experts; http://ec.europa.eu/health/documents/pharmaceutical-committee/stamp/index_en.htm).
- Ensuring that the project will leave a legacy of a stakeholder engagement process that will help implementation of MAPPs after completion of this project.

With reference to bullet #4 above, the ADAPT-SMART consortium is aware that a number of important decision makers and stakeholders are not represented among the consortium partners. Specifically, there is an absence of representation of payers, prescribers, medical societies and SMEs. This potential deficiency will be addressed in the course of the project:

- Payer involvement will be assured through the European Social Insurance Platform (ESIP), ESIP's Medicine Evaluation Committee (MEDEV), and the International Association of Mutual Benefit Societies (AIM). The collaboration with these organisations will be coordinated by the current chair of MEDEV.
- The contribution and involvement of prescribers and medical societies will be ensured through the EMA's existing Healthcare Professionals' Working Party (HCPWP), a network of over 20 European healthcare professionals' organisations that was established in 2013.
- SMEs, for which MAPPs may be of considerable interest, will be involved through outreach to their trade organisations EuropaBio (The European association for bio-industries) and EBE (European Biopharmaceutical Enterprises).

The organisations mentioned above will be part of the Stakeholders Network (see Section 3.2) and will be invited to contribute to the development/comment on documents, invited to attend workshops and other meetings as applicable, and be involved in scenario designs.

It is acknowledged that advanced therapy medicinal products (ATMPs) may create specific challenges for MAPPs from many perspectives (regulatory, HTA, payers). In light of the expectation that ATMPs will make up a sizable fraction of new products coming to market in the near to mid-term future, ATMP specific challenges will be addressed where applicable (e.g. issues of long-term surveillance, pricing and reimbursement for high cost, one-time interventions like gene-therapies, etc). At least one scenario

design will be on an ATMP (see WP2).

1.4 Ambition

Implementation of MAPPs implies evolution of the current development, licensing and healthcare delivery/access paradigms and a new quantity and quality of interaction between all stakeholders and decision makers - as described in detail in Section 1.3.

The project therefore aims to move beyond the state-of-the-art by identifying what is needed to address potential future barriers to MAPPs pathways, and to align approaches from policy makers, regulators, HTA bodies, payers, patients and prescribers with the evidence generated during development.

This project is unique in the respect that it is the most comprehensive attempt yet to involve all stakeholders in identifying relevant MAPPs activities, creating a knowledge repository and identifying scientific challenges and potential research and implementation activities that address medical needs (also in light of the 2013 update of the Priority Medicines for Europe and the World report (ref. 5), which provides a gap analysis in treatments needed) and create the right incentives for public and private actors to move beyond current pathways.

References

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2. IMPACT

2.1 Expected Impacts:

The consortium anticipates that its work will have impact on at least three distinct levels.

a) At the level of public health, health systems, and pharmaceutical R&D

The mission of the ADAPT-SMART consortium is to facilitate and accelerate the availability of MAPPs. In turn, the goal of MAPPs is to foster access to beneficial treatments for the right patient groups at the earliest appropriate time in the product life-span in a sustainable fashion.

It is expected that successful completion of the project will:

- Help addressing the ‘access versus evidence conundrum’ (as described above) and have a positive impact on public health by contributing to pathways that aim to provide patients with timely access to beneficial treatments;
- Contribute towards solutions to ensure sustainability of both the health care systems and the R&D investments and processes (for large and small companies);
- Help drive (re-)investment in R&D in under-researched unmet medical needs areas (e.g. due to lack of economic incentives and/or uncertainty about pathways or evidence requirements).

b) At the level of decision makers’ interactions and alignment of processes and goals

It is expected that successful completion of the project will:

- Support better methods for alignment of decision makers in patient organisations, industry R&D, regulatory agencies, government, HTA bodies, payers, and prescribers, with regard to their information needs, acceptance of uncertainties, timing of decision making and the balancing of interests;
- Provide actionable advice/recommendations and information to other actors in the health care environment;
- Help to realise a seamless pathway for beneficial treatments to patients.

c) At the level of (IMI and other organisations’) research strategy

It is expected that successful completion of the project will provide:

- Actionable advice/recommendations to IMI on how to best leverage results from past/current projects, thus optimising private and public investments;
- Concrete proposals for future IMI and non-IMI collaborative research projects;
- A platform for coordination with other relevant initiatives to create synergies and complementarity between their research activities;
- Synthesis of lessons from pilot projects and case studies with relevance to MAPPs.

All activities will aim at addressing three major barriers:

- Misunderstandings about the objectives of MAPPs or pre-conceptions about its impact
- Lack of willingness from one or more key decision-makers / stakeholders to engage in the MAPPs process;
- Lack of compliance with MAPPs principles on the part of one or more decision makers, resulting in loss of trust between stakeholders.

2.2 Measures to maximize impact

a) Dissemination and exploitation of results

A key objective of the CSA is to achieve consensus or, at least, agreement on acceptable compromises and future activities in this multi-stakeholder field of actors with (seemingly) conflicting roles. Given that the key actors in the healthcare environment are represented in the consortium and the stakeholder network, all agreed outcomes from this CSA will have been based on input from all relevant stakeholders. All results, conclusions, recommendation, etc. from this project will be placed in the public

domain (see below).

This is expected to ultimately result in a high degree of acceptance by all stakeholders. The output and recommendations from the CSA will be widely disseminated and have sufficient visibility to ensure relevant impact.

Methods for dissemination include websites, press releases, joint publications, workshops and, where appropriate, scenario design sessions involving different stakeholders. Please consult the work packages (Section 3.1) for more detailed description. For all publications, we will strive for 'gold' open access publishing (article immediately available on the website of the publisher) to reach the broadest audience possible. Beyond these "push" tools the consortium will be mindful to systematically and continually engage in face-to-face interactions with a wide range of stakeholders and decision makers and to reach out to wider constituencies of consortium partners.

In order to reach specific target groups (e.g. professional societies, large academic institutions), presentations will be given at external conferences organised by these groups. Attendance at these meetings will be spread throughout the EU, to ensure full participation of target groups in Central, Eastern, and Southern Europe.

Slide decks prepared by consortium partners on MAPPs relevant topics will be made widely available, to allow external presenters ("information multipliers") to avail themselves of high-quality presentation material on MAPPs.

b) Communication activities

In the work plan (Section 3.2) we describe a number of activities for promoting the project and its findings, these include:

- Workshops at the level of the different work packages (e.g. D2.03, D2.07, D3.02);
- Simulations/scenario design (D2.04);
- Building and maintaining a public project website (D4.04);
- Building a list of relevant stakeholders (D4.05);
- A structured approach through external communications, by formulating a plan which will also describe how different groups will be approached (D4.06);
- Press releases (D4.10).

3. IMPLEMENTATION

3.1 Work plan — Work packages, deliverables and milestones

The ADAPT-SMART consortium consists of three work packages which jointly address the challenges described in Section 1. An overview of the project and its components can be seen in Figure 1. The first work package (WP1) is more focused on methodological challenges, and therefore scoped in a slightly different way. This work package will play a role as an important framework for the rest of the project.

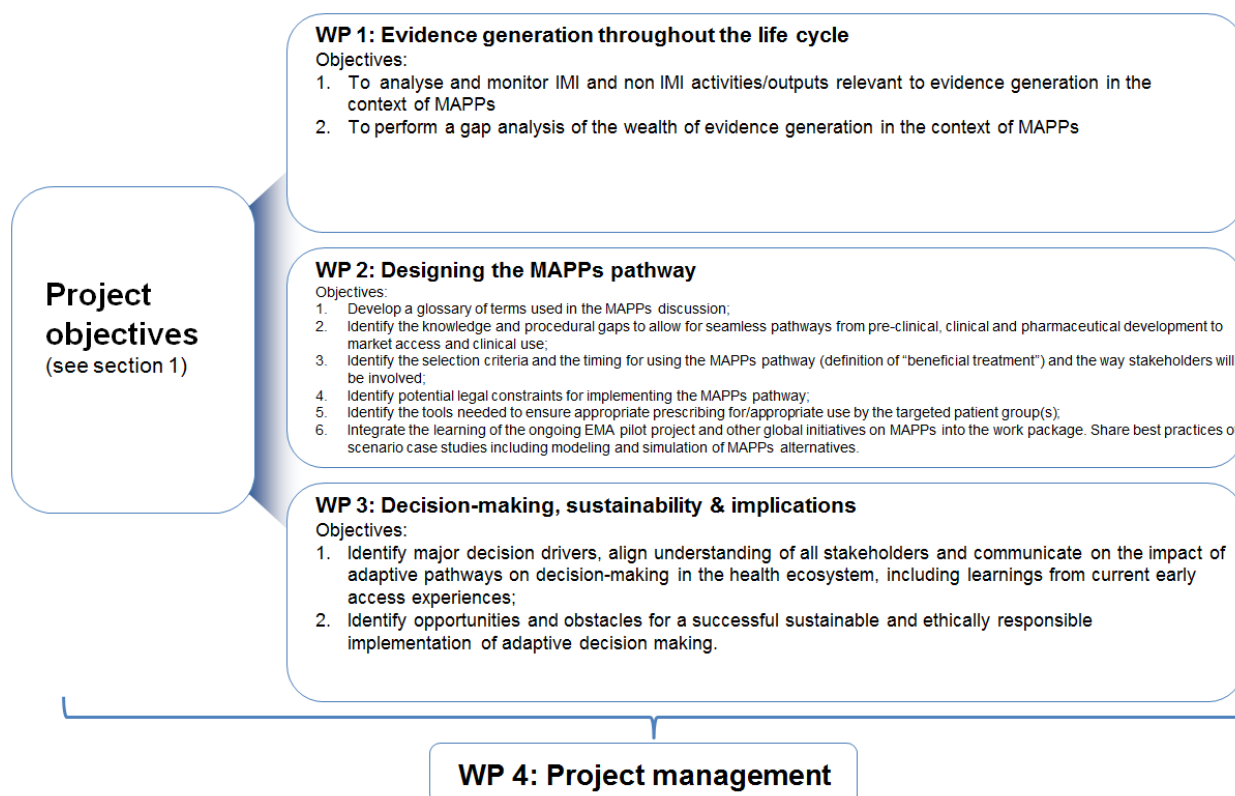


Figure 1 – Overview of the work packages

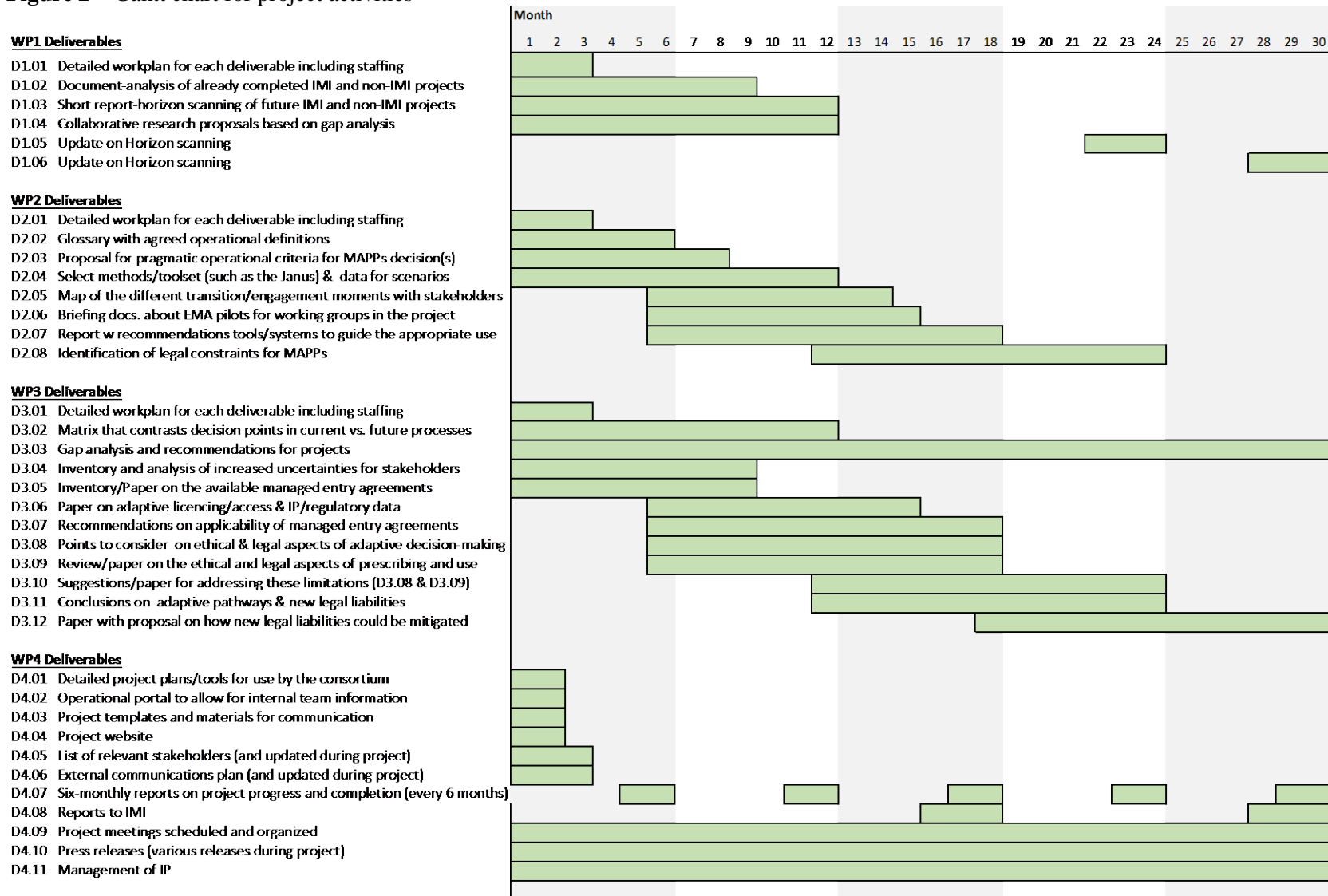
The level of detail in the description of each work package reflects the nature of work that will be conducted (but all will deliver detailed implementation plans as a first deliverable):

- Work Package 1 will enable or inform a number of activities in Work Packages 2 and 3. It will consider various facets of particular elements, which cannot be dissociated or broken down at this stage of the project before a preliminary mapping of data sources and tools/methodologies is carried out.
- Work Package 4 is related to project management and daily operations, which can be anticipated and planned.

The number and type of activities as well as their scope has been carefully assessed and prioritised against time and resources, in particular for the first half of the project term. The Navigator Group (see 3.2.3) will periodically review the work plan and priorities in light of milestones completed and outputs of the dialogue with the Stakeholders network (see 3.2.6).

One of the first activities of the project is to create a ‘detailed work plan’ (D1.01, D2.01, D3.01, and D4.01). This work plan entails a more detailed description, per deliverable, of the timelines, responsibilities, cross-work package links, risks and risk mitigation strategies. This deliverable will be finished in month 3 of the project. The kick-off meeting (probably held after 2 months) will be an important moment to discuss the drafts of these work plans before they are finalized. An initial Gantt chart for the project deliverables described in this project overview is in Figure 2 (next page). This Gantt chart will be updated with the outputs of the ‘detailed work plan’.

Figure 2 – Gantt chart for project activities



Work package number	1	Start Date or Starting Event	M1
Work package title	Evidence generation throughout the life cycle		

Objectives

1. To analyse and monitor IMI and non-IMI activities/outputs relevant to evidence generation in the context of MAPPs.
2. To perform a gap analysis of the wealth of evidence generation in the context of MAPPs.

Description of work (where appropriate, broken down into tasks), lead partner and role of participants
IMPORTANT: *This is not an implementation project but a Coordination and Support Action which has specific objectives but is not aimed at delivering new methods/methodologies.*

Leads: AZ, NICE

Expertise brought in by consortium members (public and private): methodologist in preclinical sciences, statistics and epidemiology, translational science, clinical pharmacology, big data analysis, modelling/pharmacometrics experts, chemistry, manufacturing and control (CMC), health outcomes, diagnostics, pharmacovigilance.

1-2: The review performed to achieve the 2 objectives, will address the following items:

- a. Review of relevant and reliable data generation throughout the product life cycle:
 - Practical issues around data generation;
 - Progressive validation of biomarkers;
 - Progressive validation of patient reported outcomes;
 - Non-traditional methods of data generation, e.g. mHealth, eHealth, registries, data mining in electronic health records, data mining from online communities (e.g. IMI WEB-RADR, social media);
 - Data standards and interoperability;
 - Generating evidence of effectiveness;
 - Continuous data generation.
- b. Review of tools and methods to support evidence generation and data interpretation throughout the product life cycle:
 - Pre-clinical evidence impact on primary or secondary endpoints;
 - Predictive preclinical tools for benefit/risk assessment;
 - Tools for stratifying patient populations;
 - Use of diagnostic tools;
 - Determination of linkage between patient relevant outcomes and clinical endpoints;
 - Methods that could help optimise drug development, e.g. non-conventional RCTs and non-randomised clinical trials (e.g. basket studies, treatment matching studies), modelling and simulation and extrapolation across treatment population, indications and molecules;
 - Methods to enable evidence generation for personalised treatment combinations;
 - Methods for estimating the value of information at a given time point during the product life-cycle;
 - Development and validation of algorithms for patient allocation to (combination-) treatment;
 - Methods for determining uncertainty, including patient preferences and values;
 - Methods for adjusting for biases of real-world data.

c. Biopharmaceutical development/CMC aspects at different milestones in the product life cycle.

2. Conduct a gap analysis of MAPPs enablers to help informing future research activities

Based on the review detailed above, the gap analysis should not only identify why/how existing methods could be better used, but will also identify gaps, e.g. tools and methods that would need to be developed (further).

Deliverables (brief description and month of delivery)

D1.01 Work plan

Identification of a detailed work plan for each deliverable agreed by WP1 partners and with the Navigator Group, at **Month 3**, which should help guiding the work to achieve the objectives.

Leads: NICE, AZ

D1.02 Document

Analysis of already completed IMI and non-IMI projects and their outputs, and translation into outcomes with the release of a specific document in **Month 9**.

Leads: HAS, HLU, NICE

D1.03 Short report

Horizon scanning of future IMI and non-IMI projects with the release of a summary of the findings, via a short structured and commented overview report, **on a yearly basis** (D1.05, D1.06).

Leads: EPF, BI, NICE

D1.04 Collaborative research proposals & recommendation

Proposals and recommendations based on the Gap analysis for projects addressing evidence generation in an adaptive environment **in Month 12**. These recommendations can be revisited during the project on an annual basis and will be input for discussions in other WPs (e.g. for D3.03).

Leads: NICE, IPSEN, EMA

Work package number	2	Start Date or Starting Event	M1
Work package title	Designing the MAPPs pathway		

Objectives

1. Develop a glossary of terms used in the MAPPs discussion;
2. Identify the knowledge and procedural gaps to allow for a seamless pathway from pre-clinical, clinical and pharmaceutical development to market access and clinical use;
3. Identify the selection criteria and the timing for using the MAPPs pathway (definition of “beneficial treatment”) and the way stakeholders will be involved;
4. Identify potential legal constraints for implementing the MAPPs pathway;
5. Identify the tools needed to ensure appropriate prescribing for/appropriate use by the targeted patient group(s);
6. Integrate the learning of the ongoing EMA pilot project and other global initiatives on MAPPs into the work package. Share best practices of scenario case studies including modelling and simulation of MAPPs alternatives.

Description of work

IMPORTANT: This is not an implementation project but a Coordination and Support Action (CSA) with specific objectives, but is not aimed at delivering new methods/ methodologies.

Leads: BMS, TI PHARMA

Expertise brought in by consortium members (public and private): epidemiologists, regulatory, HTA/access, commercial/marketing, labelling, pre-clinical/clinical development, CMC, healthcare policy makers, pharmacovigilance, medical affairs.

All activities will incorporate information from literature, past and on-going IMI and non-IMI projects. The activities include:

Work plan (D2.01)

At the start of the work package a detailed work plan for the work package, including staffing, for each of the work package deliverables, will be created.

Glossary of terms (D2.02)

In order to facilitate the discussion on MAPPs implementation and future projects, a glossary will be developed with agreed operational definitions of the terms used in international literature and all further communications on MAPPs during and following this CSA. Input will be requested from other IMI projects such as GetReal and from non-IMI projects, and from the different ADAPT-SMART WPs.

Selection criteria for MAPPs (D2.03)

Define and/or develop/propose pragmatic operational criteria for the respective decision(s) to use the MAPPs pathway and the timing and the stakeholders needed for this decision. The report “*Priority Medicines for Europe and the World, 2013 update*”² will be used as a starting point. The feasibility of a successful adaptive development will be taken into account, such as the definition of a disease, clinically relevant endpoints, identification of patient groups and the type of comparator used.

Knowledge gaps seamless pathway (D2.05)

Map out, within the current EU development and access pathways, the different transition/engagement moments with stakeholders, and identify the information and data needs of these stakeholders at each of these moments. Transition/engagement moments are, for example, orphan drug designation request,

² http://www.who.int/medicines/areas/priority_medicines/MasterDocJune28_FINAL_Web.pdf

scientific/HTA/payer advice(s), clinical trial approval, marketing authorization, HTA decision(s), reimbursement decision(s) and uptake in formularies or prescription guidelines, and patient involvement. We will further explore if these engagement moments should be different for a MAPPs pathway. In collaboration with other WPs, we will develop a set of MAPPs principles, including the value/efficiency of information/data: guidance on what information/data to be generated, what tools to apply in what situations, what tools/methods need to be developed, and when to generate information/data. This also includes: review and learn from other development/approval pathways (e.g. US Breakthrough Therapies), and design a functional and flexible model for an adaptive pathway in which all stakeholders are served with relevant information at appropriate time points in the development and during the life cycle of the product. Where appropriate, the development of companion diagnostics should be considered in designing this pathway.

Progressive information collection and stakeholder feedback (the iterative component of MAPPs) (D2.05)

Map out in which way all information/data collected in later phases of the product's development, during the regulatory review, and during the actual life cycle of the product could feed back into the stakeholders involved in the different stages

EMA pilots and other initiatives (D2.04 & D2.06)

The WP will review the available lessons of the EMA pilots and other initiatives on an ongoing basis, and decide how these lessons can be integrated in the work package or in one of the other work packages. It will also investigate and identify toolsets and methodologies for quantitative analysis (e.g. the JANUS program from NEWDIGS), including the stakeholders' willingness and possibilities to share datasets to perform future scenario studies in order to facilitate stakeholder engagements. For the latter, the consortium could eventually apply the NEWDIGS case-based "scenario design" methodology to explore stakeholder-specific benefit, risk, and uncertainty trade-off decisions and associated impacts throughout the life-span of the product, if possible within the timeframe of this CSA. Scenario designs (exact number to be determined, based on available time and support) will be conducted on either recently authorised products (historic cases) or hypothetical cases modelled on historic cases. At least one scenario will be based on an ATMP.

Appropriate market utilisation for the targeted patient group (D2.07)

Review of current tools and systems to guide the appropriate use by the targeted patient groups, both at the European and national level; tools such as the Summary of Product Characteristics (SmPC), the patient leaflet, delivery status, prescription guidelines, other drivers of utilisation will be included in the work. This review will result in proposals for further study and in recommendations to the national health systems, EMA, European Commission, health care providers and patients.

Legal constraints in regulatory and access legal framework MAPPs (D2.08)

Ideally, the MAPPs pathway should be integrated within the current legislative frameworks (European and nationally). Taking into account the work of the STAMP group, a scan is to be performed for detecting potential legal constraints for the implementation of eventual pilots and the ultimate MAPPs pathway.

Deliverables (brief description and month of delivery)

D2.01 Work plan

Detailed work plan for each deliverable including staffing in **Month 3**.

Lead: TI PHARMA, BMS

D2.02 Glossary of terms relevant to MAPPs:

Draft glossary in **Month 2**, to be discussed within all WPs and signed off by Navigator Group in **Months 2 – 6**; regularly updated during the project.

Lead: TI PHARMA, JPNV

D2.03 Selection criteria for MAPPs:

Briefing document in **Month 4**; workshop in **Month 6**; report with recommendations in **Month 8**.

Lead: TI PHARMA, EURORDIS, MSD

D2.04 Scenarios

Select methods, toolset (such as the Janus program) and datasets to perform scenario studies in order to facilitate stakeholder engagement. **Month 12**. Report of scenario design conducted based on NEWDIGS approach **Month 18** (tentative, to be determined).

Lead: EMA, MIT, BMS

D2.05 Seamless pathway model/feedback:

Workshop in **Month 12**; report with recommendations in **Month 14**. Workshops in collaboration with WP3.

Lead: TI PHARMA, EMA, ELI LILLY

D2.06 EMA pilots lessons

Briefing documents during project about EMA pilots to relevant leads of the working groups in the project along the 30 months of the CSA. Establish mechanism for sharing and implementing lessons in **Month 15**.

Lead: EMA, AMGEN, MIT, ZIN

D2.07 Appropriate use:

Briefing document in **Month 12**; workshop with stakeholders in network in **Month 16**; report with recommendations in **Month 18**. Workshop with WP3 (deliverable D3.09).

Lead: EPF, UCB, TI PHARMA

D2.08 Legal constraints MAPPs:

Report in **Month 24**, after reviewing outputs from WP2 and WP3.

Lead: TI PHARMA, BMS

Work package number	3	Start Date or Starting Event	M1
Work package title	Decision-making, sustainability and implications		

Objectives

1. Identify major decision drivers, align understanding of all stakeholders and communicate on the impact of adaptive pathways on decision-making in the health ecosystem, including, based on learnings from current early access experiences:
 - medicines development (efficiencies/inefficiencies);
 - economic and health care resource (e.g. pricing arrangements, risk-sharing, effective patient access and business cases for sponsors);
 - management and reduction of uncertainties over time (key success factors for sponsors, regulators, payers, policy makers and patients);
 - ethical implications for patients and clinicians;
 - intellectual property and regulatory data protection;
 - legal liabilities for all decision makers;
 - legal issues around personal data protection.

2. Identify opportunities and obstacles for a successful sustainable and ethically responsible implementation of adaptive decision making, including:
 - incorporating MAPPs enablers delivered by research initiatives including IMI into research, regulatory, coverage and reimbursement, and medical practice;
 - recommending IMI2 projects and work packages in disease-focused IMI2 projects which address missing enablers of adaptive decision-making.

Description of work (where appropriate, broken down into tasks), lead partner and role of participants
IMPORTANT: *This is not an implementation project but a Coordination and Support Action which has specific objectives but is not aimed at delivering new methods/methodologies.*

Leads: SARD (Genzyme), UOXF

Expertise brought in by consortium members (public and private): intellectual property, regulatory, clinical development, HTA, pricing and reimbursement/market access, medical affairs, communication, compliance, ethics (committees), personal data protection, liability/legal departments.

On the input side: All activities will incorporate information from literature, past and on-going IMI and non-IMI projects, interviews with key decision makers and stakeholders, as well as learnings from current early access experiences.

On the output side: Each theme will be subject to a cross-stakeholder workshop (organized with WP2 where appropriate) to confirm joint understanding and deliver recommendations for further actions needed to evolve towards adaptive decision making, including new collaborative research initiatives.

1. Mapping economic, health care resources, business impact

The consortium will aim at understanding the impact of adaptive decision-making on the economics of the health ecosystem. This will be achieved by mapping: lessons from existing early access schemes, managed entry agreements and pricing arrangements that would fit the needs of different stakeholders and their applicability in the context of adaptive approaches, prospects for adaptive/flexible pricing and reimbursement (incl. assessment of flexibilities of the current selected pricing and reimbursement systems), efficiencies and inefficiencies of adaptive pathways for medicines development and business

cases for sponsors. This work will also address issues associated with the sustainability of the workload under MAPPs for individual stakeholders. The mapping will support aligned understanding and inform multi-stakeholder reflection and recommendations on how barriers and gaps can be addressed and opportunities exploited to maximize timely access for patients to beneficial treatments. The conclusions will be tested in the scenario design sessions in WP2.

2. Management and reduction of uncertainties

Successful management and reduction of uncertainties will be a key success factor for implementation of adaptive decision making for sponsors, regulators, payers, policy makers and patients. This activity will aim at identifying enablers of managing and reducing uncertainty, defining ways forward for their implementation in research, regulatory, HTA, payers, policy makers and medical practice or their development in the frame of IMI and other research or policy initiatives. This will include criteria for timely exit strategies/adaptive disengagement (e.g. price/reimbursement changes, disinvestment). The conclusions will be tested in scenario design sessions in (D2.04).

3. Intellectual property and regulatory data protection

Premature loss of exclusivity due to an early but narrow initial indication - if not counterbalanced by other incentives - might become problematic for sponsors and for overall sector competitiveness. Activities of the consortium will aim at mapping and understanding the impact of adaptive licencing and adaptive access on IP and regulatory data protection periods and identifying counter-measures and implementation pathways.

4. Legal and ethical implications

MAPPs pathways may either exacerbate or raise new problems and opportunities from the patients' and clinicians' point of view: e.g. appropriate prescribing and use by target groups (criteria for decision making process/based on outputs from WP2), personal data protection/informed consent to treatment and maintenance of equipoise in clinical research. Activities of the consortium will aim at mapping all questions, identifying examples of good practices from comparable situations, holding workshop with patients, healthcare providers/clinicians, and decision makers and making recommendations, as input to scenario design sessions in WP2 (joint activity with WP2).

5. Legal liabilities for all decision makers (if possible within the 30-month timeframe and if appropriate expertise made available)

Taking note of the work of the STAMP group, the consortium will evaluate whether adaptive pathways would create any new legal liabilities for any decision makers in the process of development, licensing and access associated with e.g. evaluating risks and benefits in adaptive pathways in initial or subsequent indications.

Deliverables (brief description and month of delivery)

Implementation roadmap

D3.01 Detailed work plan for each deliverable including staffing in **Month 3**.

Lead: SARD (Genzyme), UOXF, NICE

Mapping economic, health care resources, business impact

D3.02. Matrix that contrasts decision points in current vs. future processes by stakeholder groups and implications for a roadmap for implementation (**Month 12**).

Incl.: Workshop to align understanding of the scientific and technological opportunities (**Month 7**)

Lead: SARD (Genzyme), UOXF

Management and reduction of uncertainties

D3.03. Gap analysis and where appropriate recommendations for projects addressing enablers of decision making in an adaptive environment (e.g. managing uncertainties at the HTA level) (Interim reports in

Months 6 & 18, Final report in Month 30). Complementarity with D1.04 will be checked.

Lead: SARD (Genzyme), UOXF

D3.04. Inventory and analysis of increased uncertainties for patients and other stakeholders and the issues these raise (**Month 9**)

Lead: SARD (Genzyme), UOXF

D3.05. Inventory/Paper on the available managed entry agreements, including pricing models and their experiences as judged by the different stakeholders (incl. assessment of flexibilities of current selected pricing and reimbursement systems) (**Month 9**)

Lead: SARD (Genzyme), ZIN

D3.07. Recommendations on applicability of managed entry agreements and pricing arrangements to possible adaptive scenarios (**Month 18**)

Lead: SARD (Genzyme), ZIN, Pfizer

Intellectual property and regulatory data protection

D3.06. Position paper on the impact of adaptive licencing and adaptive access on IP and regulatory data protection periods and recommendations on counter-measures and their implementation pathway (**Month 15**)

Lead: Pfizer

Legal and ethical implications

D3.08. Points to consider document on ethical and legal aspects of adaptive decision-making and recommendations on how these can be addressed (**Month 18**)

Lead: UOXF

D3.09. Review/paper on the ethical and legal aspects of prescribing and use by target populations including exit strategies and adaptive disengagement (**Month 18**) based on input from D2.07.

Lead: UOXF

D3.10. Suggestions/paper for addressing these limitations and recommendations for further research (**Month 24**)

Lead: UOXF

Legal liabilities for all decision makers (if possible within the 30-month timeframe and if appropriate expertise made available)

D3.11. Conclusions on whether adaptive pathways would create any new legal liabilities to all decision makers in the process of development, licencing (**Month 24**) (if resources available)

Lead: TBD

D3.12. If necessary, paper with proposal for how new legal liabilities could be mitigated (**Month 30**)

Lead: TBD

Work package number	4	Start Date or Starting Event	M1
Work package title	ADAPT-SMART Operational Project Management		

Project coordination

WP4 deals with the coordination, management, (internal and external) communication and organizational aspects of the project. The work package will be led by TI Pharma (the Coordinator), in close collaboration with and with input from the EMA, the Project Leader, and under the supervision of the Navigator Group. The overall task of WP4 is to provide overall project management support in order to ensure the completion of the project's deliverables in a timely manner. Regular interaction will take place with the leaders of the other work packages. The project management also supports the internal and external communication, the latter, also, in close collaboration with, and support from, the consortium participants. Each work package is responsible for project management at the WP level.

Objectives:

1. Support and monitor the effective execution of the work plan by providing management tools for the monitoring of deliverables, milestones and finance, enable collaboration between different work packages, and reporting to the Navigator Group and IMI JU office as required;
2. Organize/prepare meetings for project governance;
3. Keep partners and European and global stakeholders informed about project progress and manage key interactions of consortium;
4. Plan and coordinate the broader external communication;
5. Manage intellectual property rights and deriving value of foreground information generated (where applicable).

Description of work (where appropriate, broken down into tasks), lead partner and role of participants
IMPORTANT: This is not an implementation project but a Coordination and Support Action which has specific objectives but is not aimed at delivering new methods/methodologies.

Leads: TI PHARMA

Expertise brought in by consortium members (public and private): project management, communication, public affairs, scientific writing.

Description of work (incl. deliverables).

1. Project management / governance support

The governance structure and management procedures are described in Section 3.2.

WP4 will support the ADAPT-SMART consortium by providing scientific, governance, and management direction to the project. This also includes facilitating information exchange among work packages, supporting management meetings, coordinating inter-relationships/synergies and external outreach. WP4 will help ensure that the consortium's contractual duties are executed: the WP will advise and guide all participants on how to comply with the IMI JU regulations and their contractual and legal requirements. Furthermore, to monitor the effective execution of the work plan, WP4 will provide management tools for the monitoring of deliverables, milestones and finance, reporting to the IMI JU office as required. This will help ensure that all contributors abide by the "good practice" of resources management as presented in the IMI Financial Guidelines.

For facilitating projects, TI Pharma has built a (proprietary) platform, called "TI Plaza". This platform has been successfully used by more than 75 public-private research consortia over the years. This dedicated project space will be customized for the ADAPT-SMART consortium and can deliver:

- Tracking of all contact- and other details of project members;
- Customized milestone tracking;
- A safe data repository (for storage and exchange of (research) data, meeting announcements,

meeting- and other reports, literature, posters, presentations, etc.);

- A meeting planner and e-mail tool, both connected to all project members;
- An automated procedure for publication approval and approval of data release (customizable).

If needed (and possible), the project space can be further customized for optimal support of the consortium.

D4.01 Detailed project plans/tools for use by the consortium (Lead: TI Pharma, M2)

T4.01.1	Generate Gantt chart /detailed descriptions of project and milestones	TI Pharma	M2
T4.01.2	Generate more detailed project plan with input from participants	TI Pharma (L), input from participants	M2
T4.01.3	Distribute tools to be used by all project managers/WP leads for tracking, so that reporting of progress is consistent	TI Pharma	M2

D4.02 Operational portal (TI Plaza) to allow for internal team information (Lead: TI Pharma, M2)

T4.02.1	Make inventory of project needs	TI Pharma	M1
T4.02.2	Build project space according to requirements	TI Pharma	M1
T4.02.3	Launch portal and provide instructions to participants	TI Pharma	M2
T4.02.4	Maintain portal during project lifecycle	TI Pharma	M3-M30

D4.07 Reports on project progress and completion (Lead: TI Pharma, M6,12,18,24,30)

T4.07.1	Collect information from consortium partners according to predefined templates	TI Pharma(L), EMA, AZ, Sanofi	M5,11,17,23,29
T4.07.2	Compile information in report for reporting to WP leads and Navigator group	TI Pharma(L),	M6,12,16,24,30

D4.08 Reports to IMI (Lead: TI Pharma, M18, M30)

T4.08.1	Identify sections & accountabilities for writing the scientific report	TI Pharma(L), EMA, AZ, Sanofi	M16,28
T4.08.2	Invitations on SOFIA to enter the financial details	AZ/EMA	M17,29
T4.08.3	Collection and collation of the financial reports	AZ/EMA	M18,30
T4.08.4	Approval of budgets in SOFIA	AZ/EMA	M18,30
T4.08.5	Write scientific report	All participants	M18,30
T4.08.6	Project team approval of report	All participants	M18,30
T4.08.7	Submit report	AZ/EMA	M18,30

2. Organization of project meetings

This responsibility will include organisation of all consortium meetings, including the General Assembly, International Advisory Board, Navigator Group meetings, and any ad hoc meetings as required. These will be organised and conducted via the most appropriate channel and according to appropriate allocation of resources. Methods will include face-to-face meetings, teleconferences, video or web-conferences for group presentation in multiple locations and the drafting of any subsequent meeting reports or minutes. This activity also includes support of the meeting workshops, incl. travel support (content to be delivered by the work packages involved).

D4.09 Project meetings scheduled and organized (Lead: TI Pharma, M30)

T4.09.1	Dates scheduled for Navigator group, General Assembly and other project meetings	TI Pharma, WP leads	M2
T4.09.2	Preparation of meetings	TI Pharma, EMA, WP leads	M3-M30
T4.09.3	Facilitate meetings and reporting	TI Pharma, EMA	M3-M30

3. Informing partners and stakeholders

Activities to achieve the third objective include: managing the strategic interaction of the different stakeholders within and outside the consortium: e.g. key healthcare system stakeholders inside the EU (e.g. IMI, HTA bodies, European Commission, patient organizations, regulatory authorities, EFPIA) and outside of the EU (e.g. FDA, PMDA), in order to create awareness and provide input to the global discussion on the topics of ADAPT-SMART, and to receive feedback on general strategy and output and to translate this into implications for the work packages.

D4.05 List of relevant stakeholders (Lead: EMA, M3)

T4.5.1	Develop template for collecting information	EMA(L), TI Navigator group	M2
T4.5.2	Collect list of relevant stakeholders and background info from participants	EMA(L), TI Pharma,	M2
T4.5.3	Distribute database to consortium	EMA(L), TI Pharma	M3
T4.5.4	Update database during project	EMA (L), TI Pharma	M4-M30

4. External communication activities

Activities involve designing and implementing communication and dissemination plans as well as developing and implementing a communication strategy in collaboration with the EMA and EFPIA. For external communications the following needs to be considered:

- To ensure consistent messaging: position statement and/or key messages about ambition/objectives of this initiative that are approved by all team members and may be used by any of them if questioned about the project by external parties (e.g. media). This ensures consistent messaging.
- Exploit output as ‘white papers’ once available; e.g. issue news releases that will be sent to high impact scientific/medical journals (in collaboration with the consortium partners).

D4.03 Project templates and materials for communication (Lead: TI Pharma, M2)

T4.03.1	Develop logo and project house-style	TI PHARMA(L), EFPIA	M2
T4.03.2	Develop slide/poster/newsletter template	TI PHARMA(L), EFPIA	M2
T4.03.3	Post materials on workspace and distribute	TI PHARMA	M2

D4.04 Project website (Lead: TI Pharma, M2)

T4.04.1	Identify website needs, domain name, hosting, technical aspects	TI Pharma(L)	M1
T4.04.2	Generate website texts with input from participants	TI Pharma(L), all participants	M2
T4.04.3	Build website and launch	TI Pharma	M2
T4.04.4	Maintain website during project life-cycle	TI Pharma	M3-30

D4.06 External communications plan (Lead: TI Pharma, M3)

T4.06.1	Identify communication needs for external communication	TI Pharma(L), EFPIA, AZ, BMS, EMA, participants	M2
T4.06.2	General communication plan for external communication, incl. key messages, boilerplates, processes for approval etc.	EFPIA (L), TI Pharma, AZ, BMS, EMA	M3
T4.06.3	Maintain and regularly update plan during project lifecycle	TI Pharma (L), EFPIA, AZ, BMS, EMA	M4-30

D4.10 Press releases (Lead: TI Pharma, M30)

T4.10.1	Distribute procedure for press releases	TI Pharma(L), in coordination with all participants	M2
T4.10.2	Identify opportunities for press releases and take action (initial: press release at launch)	TI Pharma(L), EFPIA, EMA	M2-30

6. IP management

Due to the nature of the work, IP issues will probably be limited in the project. Nonetheless, all participants need to be aware of IP rules and any IP related issues need to be managed.

D4.11 Management of IP (dissemination of policy and awareness) (Lead: TI Pharma, M30)

T4.11.1	Ensure that all participants are aware of intellectual property rules, access rights and are aware of the issues pertaining to data dissemination and access rights.	TI Pharma(L)	M1
T4.11.2	Manage any emerging IP issues	TI Pharma(L)	M2-M30

Table 3.1a: List of work packages

Work package No	Work Package Title	Lead Participant No & name)	Start Month	End month
1	Evidence generation throughout the life cycle	(co-leads): 8. NICE 15. AZ	1	30
2	Designing the MAPPs pathway	(co-leads): 1.TI PHARMA 11. BMS	1	30
3	Decision-making, sustainability and implications	(co-leads): 6. UOXF 30. SARD	1	30
4	ADAPT-SMART Operational Project Management	1.TI PHARMA	1	30

Table 3.1b: List of Deliverables

Deliverable (number)	Deliverable name	Work package number	Short name of lead participants	Type	Dissemination level	Delivery date
D1.01	Detailed work plan for each deliverable including staffing	WP1	NICE, AZ	R	PU	3
D1.02	Document-analysis of already completed IMI and non-IMI projects and their outputs	WP1	HAS, HLU, NICE	R	PU	9
D1.03	Short report-horizon scanning of future IMI and non-IMI projects with release of a summary of the findings	WP1	EPF, BI, NICE	R	PU	12
D1.04	Collaborative research proposals based on gap analysis	WP1	Ipsen, EMA, NICE	R	PU	12
D1.05	Update on Horizon scanning	WP1	EPF, BI, NICE	R	PU	24
D1.06	Update on Horizon scanning	WP1	EPF, BI, NICE	R	PU	30
D2.01	Detailed work plan for each deliverable including staffing	WP2	TI PHARMA, BMS	R	PU	3

Deliverable (number)	Deliverable name	Work package number	Short name of lead participants	Type	Dissemination level	Delivery date
D2.02	Glossary with agreed operational definitions of the terms used in international literature	WP2	TI PHARMA, JPNV	R	PU	6
D2.03	Proposal for pragmatic operational criteria for the respective decision(s) to use the MAPPs pathway, the timing and the stakeholders needed for this decision. (workshop in M6, briefing document M4)	WP2	TI PHARMA, EURORDIS, MSD	R	PU	8
D2.04	Select methods, toolset (such as the Janus program) and datasets to perform scenario studies in order to facilitate stakeholder's engagement	WP2	EMA, MIT, BMS	R	PU	12
D2.05	Map of the different transition/engagement moments with stakeholders, and identify the information and data needs of these stakeholders at each of these moments	WP2	TI PHARMA, EMA, ELI LILLY	R	PU	14
D2.06	Briefing documents during project about EMA pilots to relevant leads of the working groups in the project	WP2	EMA, AMGEN, MIT, ZIN	R	PU	15
D2.07	Report with recommendations on current tools and systems to guide the appropriate use by the targeted patient groups, both at the European and national level (also input for D3.09). (workshop in M16)	WP2	EPF, UCB, TI PHARMA	R	PU	18
D2.08	Identification of legal constraints for MAPPs	WP2	TI PHARMA, BMS	R	PU	24
D3.01	Detailed work plan for each deliverable including staffing	WP3	SARD (Genzyme), UOXF, NICE	R	PU	3
D3.02	Matrix that contrasts decision points in current vs. future processes by stakeholder groups and implications for a roadmap for implementation. (workshop in M7)	WP3	SARD (Genzyme), UOXF	R	PU	12

Deliverable (number)	Deliverable name	Work package number	Short name of lead participants	Type	Dissemination level	Delivery date
D3.03	Gap analysis and where appropriate recommendations for projects addressing enablers of decision making in an adaptive environment (e.g. managing uncertainties at HTA level). (interim: M6, M18)	WP3	SARD (Genzyme), UOXF	R	PU	30
D3.04	Inventory and analysis of increased uncertainties for patients and other stakeholders and the issues these raise	WP3	SARD (Genzyme), UOXF	R	PU	9
D3.05	Inventory/Paper on the available managed entry agreements, including pricing models and their experiences as judged by the different stakeholders	WP3	SARD (Genzyme), ZIN	R	PU	9
D3.06	Position paper on the impact of adaptive licencing and adaptive access on IP and regulatory data protection periods and recommendations	WP3	ZIN, Pfizer	R	PU	15
D3.07	Recommendations on applicability of managed entry agreements and pricing arrangements to possible adaptive scenarios	WP3	SARD (Genzyme), ZIN, Pfizer	R	PU	18
D3.08	Points to consider document on ethical and legal aspects of adaptive decision-making and recommendations on how these can be addressed	WP3	UOXF, ZIN	R	PU	18
D3.09	Review/paper on the ethical and legal aspects of prescribing and use by target populations	WP3	UOXF	R	PU	18
D3.10	Suggestions/paper for addressing these limitations (from 3.08 and 3.09)	WP3	UOXF	R	PU	24
D3.11	Conclusions on whether adaptive pathways would create any new legal liabilities (if resources available)	WP3	TBD	R	PU	24

Deliverable (number)	Deliverable name	Work package number	Short name of lead participants	Type	Dissemination level	Delivery date
D3.12	Potential paper with proposal for how new legal liabilities could be mitigated	WP3	TBD	R	PU	30
D4.01	Detailed project plans/tools for use by the consortium	WP4	TI PHARMA	R	PU	2
D4.02	Operational portal to allow for internal team information	WP4	TI PHARMA	OTH	PU	2
D4.03	Project templates and materials for communication	WP4	TI PHARMA	OTH	PU	2
D4.04	Project website	WP4	TI PHARMA	DEC	PU	2
D4.05	List of relevant stakeholders (and updated)	WP4	EMA	OTH	PU	3
D4.06	External communications plan (and updated)	WP4	TI PHARMA	R	PU	3
D4.07	Six-monthly reports on project progress and completion (first in M6, then every 6 months)	WP4	TI PHARMA	R	PU	6
D4.08	Reports to IMI (first in M18, then M30)	WP4	TI PHARMA, AZ	R	PU	12
D4.09	Project meetings scheduled and organized	WP4	TI PHARMA	OTH	PU	30
D4.10	Press releases (various releases during project)	WP4	TI PHARMA	OTH	PU	30
D4.11	Management of IP	WP4	TI PHARMA	OTH	PU	30

3.2 Management structure and procedures

The holistic approach to MAPPs will be reflected in the ADAPT-SMART project architecture, which is made up of a set of components that are described in Figure 3. Individual components are described below.

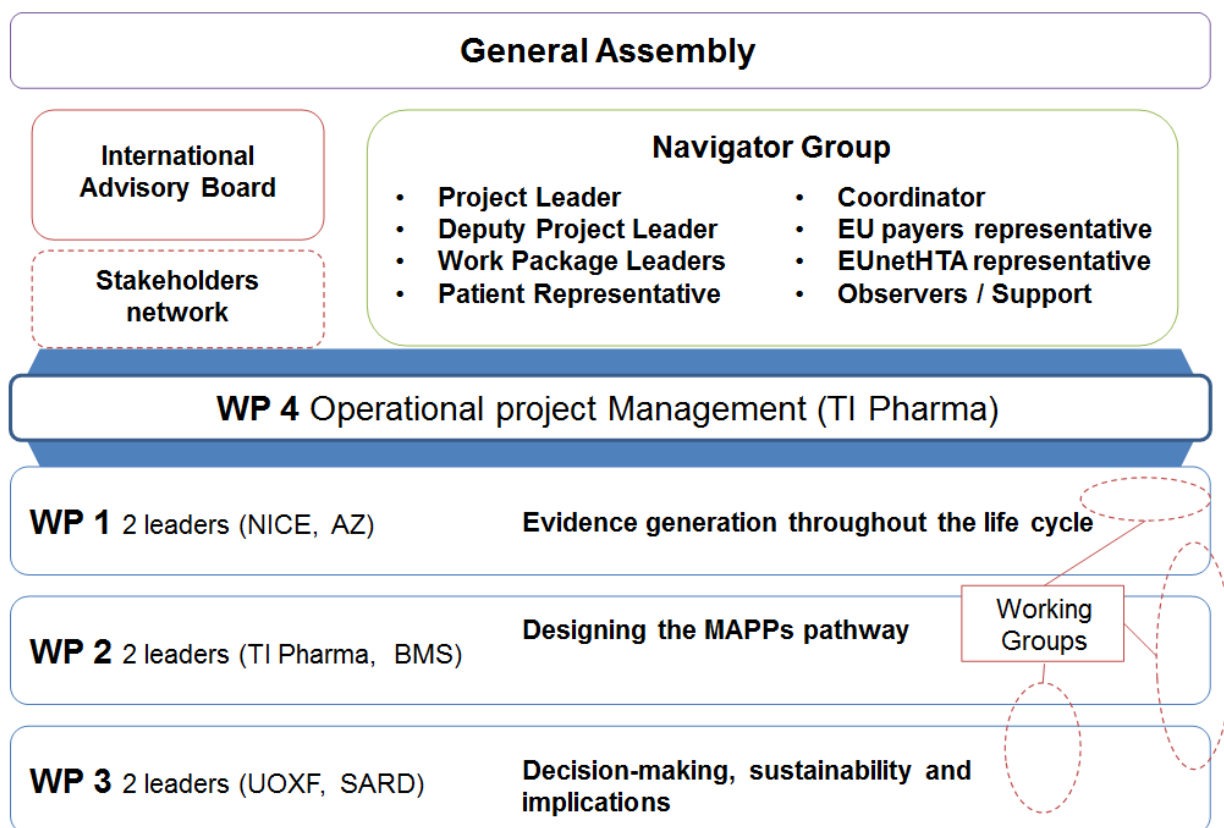


Figure 3 – Project governance

3.2.1 General Assembly

The General Assembly shall include a representative from each participant of the ADAPT-SMART consortium, with equal voting rights. The General Assembly is the highest decision making body. The General Assembly will be assisted by the Coordinator with support from other WP4 members where necessary. The General Assembly will be responsible for decisions that need to be consulted and/or decided by all Participants such as:

- Entering of new Participants in the consortium withdrawal/removal of Participants;
- Major changes in the budget allocation;
- Addition of subcontractors;
- Major changes in the work plan;
- Approval of periodic reports prior to submission to the IMI JU;
- Reviewing intended publications from participants.

The General Assembly will take decisions preferably by consensus and in any case by majority vote. Following expiry or early termination of the Project, the General Assembly shall remain in force for at least one year solely for the purpose of receiving and reviewing intended publications from participants.

General Assembly will be chaired by the Project Leader (EMA). The Deputy Project Leader (AZ) and Coordinator (TI Pharma) will act as co-chairs.

3.2.2 Project Leader, Deputy Project Leader and Coordinator.

The Project Leader (EMA) is responsible for the overall scientific and project related leadership in collaboration with the Deputy Project Leader (AZ), and the Coordinator (TI Pharma). The Deputy Project Leader is responsible for, among other things, coordinating the EFPIA efforts in the project. The

role of the Coordinator is further defined in the Grant Agreement.

3.2.3 Navigator Group

The Navigator Group is responsible for making key management decisions within the framework of the project proposal and for ensuring the effective running of the project. The responsibilities of the Navigator Group are, among others, to:

- Manage the work performed in the work packages;
- Ensure overall project progress and integration of the recommendations into reports to IMI and publications of the work packages;
- Maintain the integrated MAPPs viewpoint;
- Oversee the work the individual Work Packages and review and synthesise their work;
- Coordinate the external and internal communication.

The Navigator Group has at least 4 face-to-face or virtual meetings per year. The composition of the Navigator Group is (at launch):

- The Project Leader;
- The Deputy Project Leader;
- The Coordinator
- The Work Package leaders (both public and private) of the Work Packages 1- 4, if not already represented as (Deputy) Project Leader or Coordinator;
- One representative from the patient groups (EURORDIS and EPF will jointly nominate a representative to participate on their behalf);
- One senior representative of EU payer associations (non-voting member for financial matters in project);
- One senior representative of the EUnetHTA secretariat;
- Other consortium members may be invited to participate in Navigator Group meetings as ‘Observers’;
- Support to the Navigator Group (D4.09) will be provided by the EMA.

Navigator Group composition will reflect a balanced representation of all MAPPs stakeholders, so members may be added as non-voting members if that is valuable for the discussion.

Operational/management support for the Navigator Group is provided by the Project Management work package (Work Package 4).

When a consensus decision cannot be reached by the Navigator Group, an independent expert will be sought to mediate on the issue, as a last resort the issue will be put before the General Assembly for voting.

The Navigator Group will be chaired by the Coordinator (TI Pharma). The Project Leader (EMA) and Deputy-Leader (AZ) will act as co-chairs.

3.2.4 Working groups (ad-hoc)

Within, or between, work packages one or more ad-hoc Working Groups can be established with different stakeholders represented. If needed, working groups can be formed to address topics that occur/have to be managed in more than one work package.

Potential topics for the Working Groups are, for example:

- Provide input to identify existing/upcoming IMI and non-IMI project output;
- Give feedback on gap analysis of MAPPs;
- Provide recommendations on next steps in work on the project.

The consortium shall encourage broad exploration within Working Groups before narrowing to recommended “solutions” where needed.

3.2.5 International Advisory Board

An International Advisory Board convenes senior international leaders. This group will not directly contribute to the project work but will provide independent steer to the consortium participants to ensure due consideration of non-EU perspectives and stakeholder groups that are not represented in the consortium.

Senior leaders from the following institutions/communities may be invited to join the International Advisory Board, including:

- (non-)EU patient community
- (non-)EU regulatory community
- (non-)EU HTA community
- (non-)EU payer community
- EU-based investor /venture capital representative
- EU-based public media representative
- EU-based hospital/provider organisations

3.2.6 Stakeholders network

In addition, the stakeholder network of the participants within the EU will be involved via an outreach program as part of the communication plan. The Stakeholders network group is expected to include (but will not be limited to): completed and ongoing IMI project groups, EU health care payers, EBE, EuropaBio, organisations represented in the EMA's Healthcare Professionals' Organisations Working Party (HCPWP), academic groups, EU SMEs, CPath, FDA, PMDA, TRANSCCELERATE, CDISC, PCAST, IMI Strategic Governing Groups, EFPIA Research Directors Group, ASCO (TAPUR project), MED-C initiative, Optum Labs, EATRIS, Faster Cures, KU Leuven (CIR), 21st Century Cures proponents, and others.

3.3 Work packages

To facilitate project management and monitoring, the project has been subdivided in four work packages. The activities of the Work Packages have been described in detail in Section 3.1. Each work package has two Work Package Leaders: one co-leader from the public partners and one co-leader from the EFPIA partners, except for WP4, the project management work package, which will have only one Work package Leader. The Work Package Leaders are responsible for the execution of the work plan in their respective work packages and to ensure interactions between the different work packages. They will be responsible for reporting to the Navigator group and General Assembly on their achievements and progress.