Review Report On IMI Projects

June 2017

The work leading to these results was conducted as part of the ADAPT SMART consortium (Accelerated Development of Appropriate Patient Therapies: a Sustainable, Multi-stakeholder Approach from Research to Treatment-outcomes). For further information please refer to www.adaptsmart.eu. This paper is the result of the collective input from working group D1.02 and only reflects the views of the authors.

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
AP	Adaptive Pathways
CASMI	Centre for the Advancement of Sustainable Medical Innovation
CHMP	Committee for medicinal products for human use
CMC	Chemistry, Manufacturing, and Controls
C-PPAC	Clinical PROactive Physical Activity in COPD
D-PPAC	Daily PROactive Physical Activity in COPD
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European medicine agency
EHRs	electronic health records
FDA	US Food and Drug Administration
GP	General Practitioner
ICH	International conference on harmonisation
IMI	Innovative Medicine Initiative
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
LPLV	Last patient last visit
MAA	Marketing authorisation application
MAPPs	Medicines Adaptive Pathways to Patients
MHRA	Medicines and Healthcare Products Regulatory Agency
NICE	National Institute for Health and Care Excellence
PA	Physical activity
PBO	Placebo
PRO	Patient Reported Outcome
QA	Qualification Advice
QO	Qualification Opinion
RA	Rheumatoid Arthritis
RCT	Randomised clinical trial
RWD	Real World
RWE	Real World Evidence
SAWP	Scientific Advice Working Party
WP	Work Package

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Executive Summary

ADAPT SMART was set up as a *Coordination and Support Action* under the European Innovative Medicines Initiative (IMI). The objective of ADAPT SMART is to establish an enabling platform to facilitate and accelerate the availability of MAPPs and engage a dialogue with relevant stakeholders for the coordination of MAPPs (Medicines Adaptive Pathways to Patients) related activities. Similar to the EMA Adaptive Pathway, MAPPs seeks 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. As part of the project which is looking at which product could be worth entering the MAPPs framework (deliverables D2.05 and D3.02) according to predefined engagement criteria (deliverable D2.03), Work Package 1 plan is to conduct gap analysis, inform future research activities, and engage in knowledge management activities - all with a view to facilitate and accelerate the availability of MAPPs. To better tackle the objective, the consortium includes all relevant stakeholders.

According to its work plan, Work Package 1 (the so-called '*evidence generation throughout product life cycle*' work package) has 1) to analyse and monitor IMI and non-IMI project outputs, and 2) to perform a gap analysis of the wealth of evidence generation in the context of MAPPs. In other words, tools and methods developed by IMI and other EU projects, which could benefit MAPPs have to be identified. To this effect, a two-phase process was identified.

We first focused on mature IMI projects and according to pre-specified criteria, we selected those worth an in-depth analysis. Of the 60 IMI projects available when Phase 1 review was started, 32 were judged eligible for an in-depth review. The remaining were either put on hold pending further research, or rejected as judged not mature enough or not relevant to MAPPs. An in-depth analysis of projects' outputs was then performed according to a predefined methodology by experts in CMC, preclinical, clinical and drug access linked to real-world data, regrouped in four different workstreams. Final review and consolidated analysis was subsequently performed by the experts who performed the initial project selection.

This report summarises the findings of the initial review of IMI projects completed so far, together with a preliminary gap analysis. Several IMI outputs have been identified that could contribute the MAPPs agenda, although most of them would require some further work in order to be fully implemented in drug development, e.g. a specific/cluster of biomarkers to identify a safety issue or a target patient population.

The plan is to update this report including the gap analysis, as soon as the review of EU non IMI projects is completed, and to revisit the review of IMI projects to include projects that were initially put on hold. Final gap analysis should be completed together with proposed recommendations before end of 2017, when the project will be terminated.

1 Introduction

ADAPT SMART (www.adaptsmart.eu) is a multi-stakeholder consortium that was set up as a *Coordination and Support Action* under the EU Innovative Medicines Initiative 2 (IMI2 www.imi.europa.eu). The objective of IMI2 which started in 2014 for a 10 year period is to develop next generation vaccines, medicines and treatments, such as new antibiotics. It will build on the successes and lessons learnt under IMI's first phase which started in 2008 bringing together companies, universities, small and medium-sized enterprises, patient groups and regulators in collaborative and precompetitive projects to tackle Europe's growing health challenges, and secure the future international competitiveness of Europe's pharmaceutical industry.

The ADAPT SMART consortium comprises all relevant stakeholders in the healthcare ecosystem: patients, academics/providers, the research based industry, regulators, and health technology assessment bodies (HTABs). Some EU payers and payer organisations

although not formal partners, are willing to engage in constructive dialogue with the consortium.

The objective of ADAPT SMART is to establish an enabling platform and engage a dialogue with relevant stakeholders for the coordination of MAPPs related activities. The consortium plan is to conduct gap analysis, inform future research activities, and engage in knowledge management activities - all with a view to facilitate and accelerate the availability of MAPPs [ref: ADAPT SMART project overview[1]].

To achieve its objective, the consortium has identified four different work packages (WP), of which WP1 led jointly by a public and a private partner, has 1) to analyse and monitor IMI and non-IMI project outputs, and 2) to perform a gap analysis of the wealth of evidence generation in the context of MAPPs. Activities have been identified to tackle WP1 objectives. More specifically, the purpose of D1.02 activities was to identify: (i) already existing tools/methods that could enable MAPPs; and (ii) what tools/methods are missing and thus need development. This was done by reviewing existing and completed IMI projects in the first place. As per WP1 work plan, other EU non-IMI projects will be subsequently reviewed, and the gap analysis will be updated on a yearly basis throughout the project to capture outputs of projects that will start or complete in the future.

This report summarises the findings of the initial review of IMI projects completed so far, together with a preliminary gap analysis.

2 Methodology

2.1 Approach used to perform the review

It was agreed that to achieve the objective the review should focus first on IMI projects and once completed, looked at other EU non-IMI projects. It was also agreed that the review should be based on a set of pre-agreed criteria identified from the list of topics identified within the project description of work (DoW), and subsequently discussed and endorsed by WP1 partners. This has been broken down into workable topic areas that would allow for a comprehensive search and reporting of results within the timelines as specified in WP1 work plan.

The topic list (Table 1) as included in the DoW was separated into: (a) issues regarding data generation; (b) issues regarding tools and methods to support evidence generation; and (c) biopharmaceutical development/CMC aspects. To address all the issues, 4 different workstreams were identified, and each individual workstream had to focus on the topics according to the pre-agreed criteria.

At the start of the review, there were 65 IMI projects listed on the IMI website (www.imi.europa.eu). It was agreed that the state-of-the-art review should include these IMI projects in relation to the specific topics (Table 1). Therefore, it was proposed a phased approach where in Phase 1 the IMI projects will be reviewed. The results of this Phase 1 review could then inform a targeted literature search in order to identify scientific advances made outside of IMI-funded projects but nonetheless relevant in relation to MAPPS.

[1] http://adaptsmart.eu/wp-content/uploads/2015/09/ProjectOverview-IMI2-ADAPTSMART.pdf?_sm_au_=iJH0Lpjs7bWtMHjr

Table 1: Tools & Methods used in evidence generation studies (for HTA methodology and Regulatory)

1. *Tools for stratifying patient populations;*
2. *Use of diagnostic tools;*
3. *Linkage patient relevant outcomes and clinical endpoints;*
4. *Progressive validation of biomarkers;*
5. *Genomic profiling;*
6. *Methods to enable evidence generation for personalised treatment;*
7. *Development and validation of algorithms for patient allocation to treatment;*
8. *How to identify control groups in real-world settings*
9. *How to handle off-label use in control/treatment group real world trial*
10. *Methods for estimation of uncertainty;*
11. *Patient preference methodology;*
12. *Issues related to paediatric development*
13. *Issues related to specific study types and methodologies/approaches, e.g. pragmatic clinical trials; adaptive trials; observational studies; database and registry studies; basket trials; Bayesian trial; Modelling and Simulation - Extrapolation*
14. *Handling missing data*
15. *Methodology for Big Data- eg semantic (terminology needs clarification!); of note, there will soon be an IMI call launched so can be excluded however, work/key issues will have to be factored in ADAPT SMART review*

Phase 1:

1. Use reviews that were previously performed e.g., by EFPIA[2], CASMI[3];
2. Out of the topic list (Table 1), select the specific topics worthy of review;
3. Review IMI projects for activities related to topic list. The review should be focused on existing tools and methods that could support MAPPs. In addition, special attention should be paid to projects that include the link between different phases of the product life-cycle;
4. Interpret identified IMI projects and their relevance from an industry, regulatory, and HTA perspective;
5. Summarise review results of IMI projects.

Phase 2:

The identification of EU non-IMI projects of interest is expected to be more challenging.

6. Targeted literature review of EU non-IMI projects based on review results of IMI projects;
7. Summarise review results of EU non-IMI projects;
8. Merge both review Phases in anticipation of the gap analysis;
9. Report results of entire review including gap analysis and initial recommendations;
10. Revisit and complete the review in a year time in order to incorporate new project outputs.

Prior to performing the Phase 1 review it was agreed as a prerequisite to 1) select the different IMI projects of interest, to be analysed subsequently in depth by the 4 different workstreams, in order to mainly avoid unnecessary duplication of work within the workstreams (WS). The state-of-the-art reviews was organised as followed: 2) CMC aspects; 3) tools and methods used early in the life-cycle; 4) Clinical and HTA evidence generation during clinical development period; and 5) real world data generation (see Figure 1). As MAPPs intends to facilitate a continuum of learning across the pre- and post-authorisation phases, a focus of the state-of-the-art reviews was to identify *links* between clinical and HTA evidence generation during early product development phases and real world data collection at later stages of the product lifecycle. Therefore, the review of IMI

[2] EFPIA: European Federation of Pharmaceutical Industries and Associations (efpia.eu)
[3] CASMI: Center for the Advancement of Sustainable Medical Innovation (casmi.org.uk)

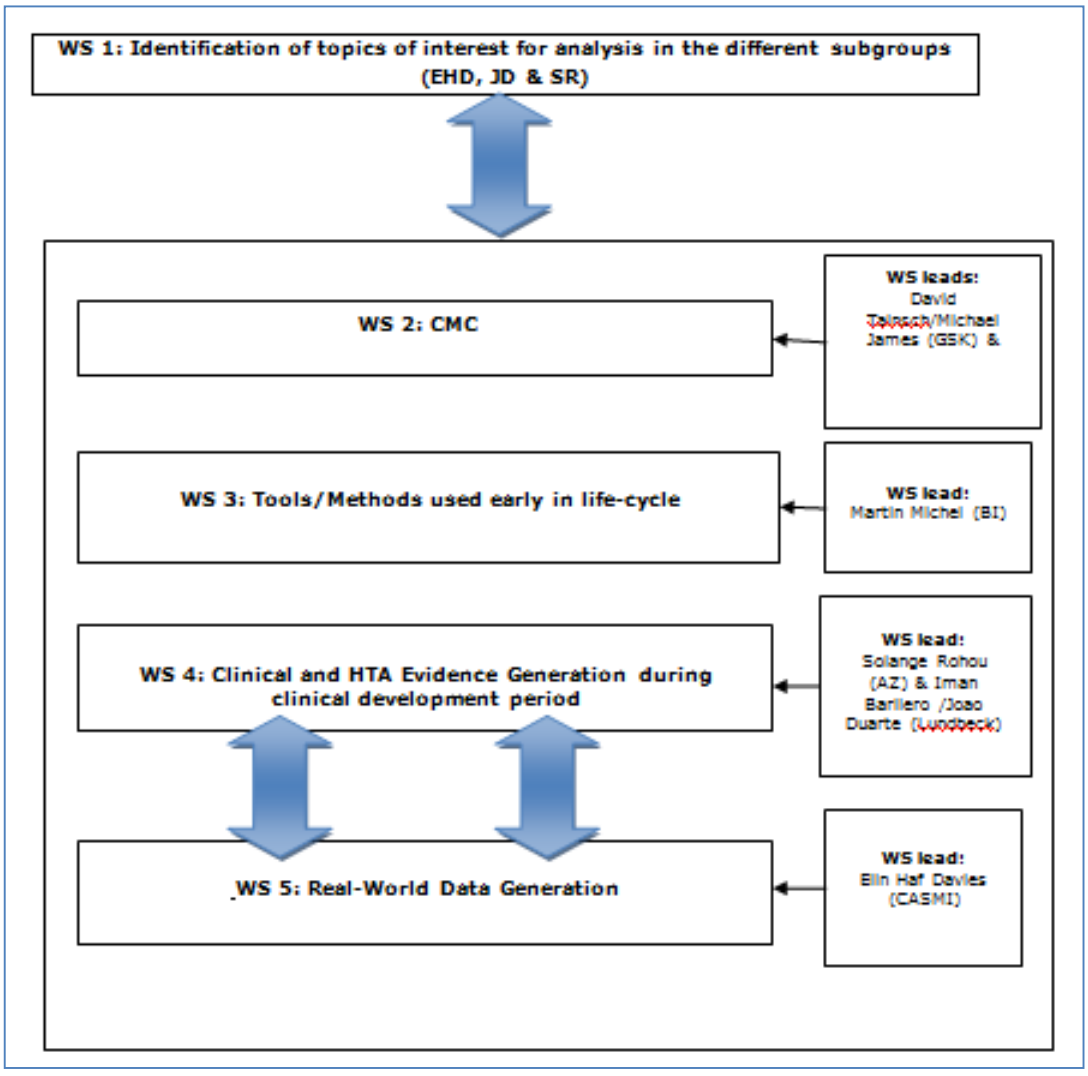
and non-IMI projects in the context of tools/methods for clinical and HTA evidence generation and tools/methods for real-world evidence generation was done from the industry, regulatory, and HTA perspectives.

To progress Phase 1 review, the following was performed:

1. All IMI projects were initially assessed by three independent assessors (Elin Haf Davies, Joao Duarte and Solange Corriol-Rohou), according to a set of criteria modified from a previous project, IMiPACT (http://casmi.org.uk/imipact-stakeholder-platform/), in order to identify suitable IMI projects to be analysed further in greater detail by each WS. WSs were given an evaluation form template to complete with each project evaluation;
2. Subsequent to the review, a consolidated analysis was performed together with an initial gap analysis;

Figure 1 outlines the chosen approach and how the selected IMI projects were reviewed by the different workstreams.

Figure 1: outline of WP1 activities



A topic lead was assigned for each workstream composed of representatives of the different stakeholders who volunteered based on their expertise:

- WS1: initial high level screening review of existing IMI projects (see section 2.2)
- WS 2: CMC (Quality)

- WS 3: Tools/Methods used Early in life-cycle
- WS 4: Clinical & HTA evidence generation during clinical development period
- WS 5: Real World Data Generation

2.2 Initial review screening

The initial high level screening review of existing IMI projects was performed by WS 1 according to the criterions seen in the excel spreadsheet (Appendix 6.2). At the time of this review, 60 IMI ongoing projects (Appendix 6.1) were considered.[4]

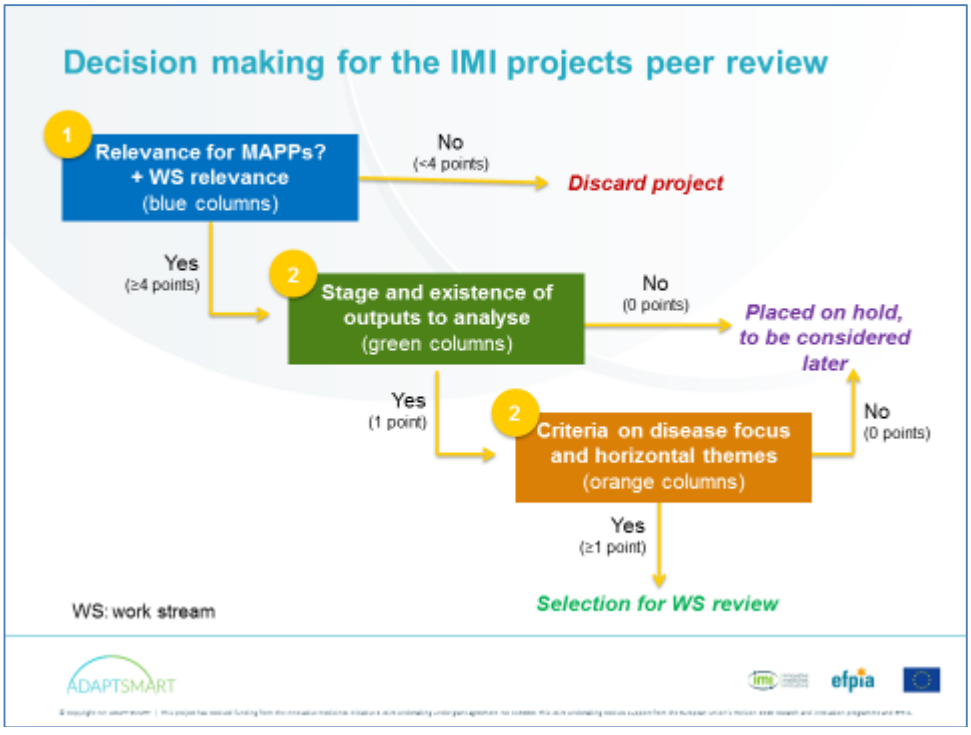
Using publically available information, the three reviewers used the excel spread sheet mentioned above and the decision tree displayed below (Figure 2) to review the projects. They subsequently performed a peer-review of their conclusion at a face-to-face meeting on May 12 in order to check the relevance of their conclusions and discuss divergences or uncertainties (which were quite limited).

The review included the following five criteria:

1. Stage and size of project;
2. Relevance of the project for MAPPs;
3. Existence of project outputs worth further analysis;
4. Whether or not the project was disease specific;
5. Project selection for WS in-depth review.

A specific selection matrix was used to track all the information (Appendix 6.2).

Figure 2: Decision Making Tree for the IMI projects peer review



[4] http://www.imi.europa.eu/content/ongoing-projects

As a result of this initial review, the selected IMI projects were transferred to the relevant WSs for in-depth evaluation (Appendix 6.3).

2.3 In-depth review

Once the initial review was completed, the different WSs (WS 2-5) performed their in-depth review using the following recommendations:

- *Analysis to be done using publicly available information, IMI project specific websites, publications, and information through personal dialogue with colleagues/project leader involved in the project;*
- *Contact colleagues that you know are part of the project you have to review, or liaise with the project coordinator;*
- *Ask for the 5 most significant achievements/publications to date as having potential valuable contribution to ADAPT SMART*.

For each IMI project, WSs had to address six questions and comment where appropriate (Table 2).

Table 2: questions raised for the in-depth review of the selected IMI projects

1. *Once your review of the project is complete, please score the project on the strength of evidence available using the following:* *1= early embryonic ideas that have not yet been tested* *2= some developed ideas with limited tested concepts* *3= moderately developed ideas and tested concepts* *4= developed and not fully tested concepts* *5= highly developed and well tested/ready to be implemented concepts* 2. *Please summarise the output(s) identified that were considered relevant to MAPPs and provide explanation.* 3. *Please specify whether the output(s) can be considered disease specific and/or transferrable to other disease areas and/or wider use? (Please clearly specify YES/ NO / NOT SURE, and provide a 4-5 sentence MAX to explain your rationale for each one)* 4. *Please score the importance of the findings as a MAPPs enabler, from 1-4, using the following:* *1= poor expected value/ contribution to MAPPs* *2= some value/ contribution to MAPPs* *3= moderate value/ contribution to MAPPs* *4= important value/ contribution to MAPPs* 5. *Do you think that the project has not included certain areas of work or addressed certain questions or issues that you consider needed/relevant? If so, what are these areas of work which could warrant further work?* 6. *Please specify any other additional comments that has not been previously stated that you think is important*

All the requested information was tracked into an evaluation form (see evaluation form template in Appendix 6.4).

It is to be noted that unfortunately the websites of the IMI projects are most often not regularly updated which is a challenge to really understand the status of the work.

2.4 Final review and consolidated analysis

Final review and consolidated analysis was subsequently performed by WS1 as planned. To this effect the outputs of all reviewed IMI projects were included into a dashboard. Outputs were subsequently grouped across to the traditional phases of drug development, quality (CMC), non-clinical, clinical trials (incl. biomarkers), and real-world data required for patient

access, along with a separate grouping according to disease area. This was done for the benefit of current understanding, and set as a basis to inform a different development paradigm. However, output analysis will be done having in mind the MAPPs pathway, a scientific concept for medicine development and data generation which allows for timely and progressive patient access to a medicine.

2.5 Review cycles

Since Phase 1 review has started, new IMI projects have emerged including those which were placed on hold by WS1 to be reviewed at a later stage. WP1 work plan already includes the need to revisit this first review, and update the gap analysis in order to provide consolidated recommendations on tools and methods to be used and/or to develop to support better the MAPPs concept at the end of the project in December 2019. Two additional review cycles are planned during ADAPT SMART project life.

3 Review findings

3.1 WORKSTREAM 1

Of the 60 IMI projects available (Appendix 6.1) when Phase 1 review was started, 32 were judged eligible for an in-depth review by the different WSs. The remaining were either parked (n=13) as judged too premature and worth the review at a later stage, or rejected (n= 15) as deemed not relevant to MAPPs. Of note, some projects were assessed by more than one WS as outputs were judged potentially relevant for more than one WS review (Appendix 6.5). Of note, two other projects were added to the list for an in-depth review: EUC²LID which was assessed by WS3 and subsequently judged of limited relevance, and ADVANCE as judged of moderate value.

Table 3 details the number of IMI projects that were assessed by the WSs.

Table 3: projects assigned to the WSs

Work stream		Number of projects assessed
WS 2	CMC Quality	3
WS 3	Tools / methods used in early life-cycle	10
WS 4	Clinical and HTA Evidence Generation during clinical development	8
WS 5	Real-World Data Generation	1
Work stream Joint Assessment		
WS 4 & 5		5
WS 3 & 4		6
WS 3, 4 & 5		1
Total number of assessed projects		32

Answers to questions 1 and 4 (Table 2) with their corresponding scoring are presented in Table 4.

Table 4: Scoring of the assessed IMI projects

Acronym	Topic Title	WS	Strength of evidence* (0-5)	Contribution to MAPPs** (1-4)
ABIRISK	Immunogenicity: Assessing The Clinical Relevance And Risk Minimization Of Antibodies To Biopharmaceuticals	4	1	1
		5	0	1

Acronym	Topic Title	WS	Strength of evidence* (0-5)	Contribution to MAPPs** (1-4)
ADVANCE	Developing A Framework For Rapid Assessment Of Vaccination Benefit/Risk In Europe	5	2	3
AETIONOMY	Developing An Aetiology-Based Taxonomy Of Human Disease - Approaches to Develop a New Classification for Neurodegenerative Disorders	4	2	2
BioVacSafe	Immuno-safety of Vaccines – New Biomarkers Associated With Adverse Events (Early Inflammation, Autoimmune Diseases & Allergy)	3	3	4
		4	4	2
BTCURE	Inflammation – Translational Research	3	2	4
		4		
CHEM 21	Chemical manufacturing methods for the 21st century pharmaceutical industries	2	3 (continuous manufacturing)	1
COMBACTE	ND4BB Topic 1: Innovative Trial Design & Clinical Drug Development - Subtopic 1B	4	4	4
COMPACT	Delivery And Targeting Mechanisms For Biological Macromolecules	2	3	4
DDMoRe	Knowledge Management – Drug/Disease Modelling	4	5	4
DIRECT	Development Of Personalized Medicine Approaches In Diabetes	4	2	2
		5		
EMIF	A European Medical Information Framework (EMIF) Of Patient-Level Data To Support A Wide Range Of Medical Research - Information Framework / Knowledge Management Service Layer	4	3	2
eTOX	Expert Systems for In Silico Toxicity Prediction	3	2	3
EU-AIMS	Translational Endpoints In Autism	4	3	3
EUC²LID	European Lead Factory – European Screening Centre	3	1	1
EUROPAIN	Pain Research	4	4	4
GetReal	Incorporating Real-Life Clinical Data Into Drug Development	4	4	4
		5	4	4
IMIDIA	Islet Cell Research	3	1	2
K4DD	Understanding And Optimising Binding Kinetics In Drug Discovery	3	2	1
MARCAR	Non-Genotoxic Carcinogenesis	3	1	1
MIP-DILI	Improving The Early Prediction Of Drug Induced Liver Injury In Man	3	2	2
NEWMEDS	New Tools for the Development of Novel Therapies in Psychiatric Disorders	3	5	3
		4	3	4
OncoTrack	Oncology – Molecular Biomarkers	3	2	2
		4	2	2
OrBiTo	In Vivo Predictive Biopharmaceutics Tools For Oral Drug Delivery	2	4	4
PHARMA-COG	Neurodegenerative Disorders	3	3	3
PREDECT	Oncology – Target Validation	3	2	1
PRO- Active	COPD Patient Reported Outcomes	4	5	1
		5	5	2
PROTECT	Strengthening the Monitoring of Benefit/Risk	4	4	3
		5	4	4
QUIC-CONCEPT	Oncology – Imaging Biomarkers	3	5	3
		4	4	3
RAPP-ID	Infectious Diseases – Diagnostic Tools	4	5	1
SAFE-T	Qualification Of Translational Safety Biomarkers	4	4	3
StemBANCC	Human Induced Pluripotent Stem (HIPS) Cells For Drug Discovery And Safety Assessment	3	1	1
SUMMIT	Surrogate Markers For Vascular Endpoints	3	2	3
		4	4	4
		5	3-5	3
Translocation	ND4BB Topic 2: Learning From Success And Failure & Getting Drugs Into Bad Bugs	3	1	1
U-BIOPRED	Understanding Severe Asthma	3	2	2
		4	2	1

***Strength of evidence – score:**

0= no relevance; 1= early embryonic ideas that have not yet been tested; 2= some developed ideas with limited tested concepts; 3= moderately developed ideas and tested concepts; 4= developed and not fully tested concepts; 5= highly developed and well tested/ready to be implemented concepts

*** Contribution to MAPPs – score:**

1= poor expected value/ contribution to MAPPs; 2= some value/ contribution to MAPPs; 3= moderate value/ contribution to MAPPs; 4= important value/ contribution to MAPPs

Eighty-five (85) outputs from the thirty-two (32) IMI projects were identified, and considered as relevant to MAPPs (Table 5). These were then grouped across to the traditional phases of drug development, CMC quality (WS2), early life-cycle (WS3), clinical development (incl. biomarkers) (WS4), and real-world data generation (WS5), along with a separate grouping according to disease area. This was done for the benefit of current understanding, and set as a basis to inform a different development paradigm such as MAPPs. However, output analysis was done with a MAPPs pathway in mind, with a scientific concept for medicine development and data generation that allows for timely and progressive patient access to a medicine.

Table 5: outputs identified by the WSs

Work stream		Number of outputs
WS 2	CMC Quality	9
WS 3	Tools / methods used in early life-cycle	24
WS 4	Clinical and HTA Evidence Generation during clinical development	47
WS 5	Real-World Data Generation	5
Total		**85**

3.2 WORKSTREAM 2

In terms of Quality Chemistry, Manufacturing and Control (CMC) nine outputs were identified under this umbrella. This aspect is important to MAPPs in order to provide assurance that the quality of the products will not be compromised by an earlier access, while assuring the flexibility needed to deliver consistent and reliable supplies in a less predictable environment.

Only three potentially relevant IMI projects were reviewed in this context, **COMPACT, OrBiTo** and **CHEM21.** After the in-depth review, only two were deemed relevant for MAPPs.

The goal of the **COMPACT** (www.compact-research.org) project is to shed new light on the obstacles that biological molecules such as proteins, peptides or nucleic acids, (which are known as biopharmaceuticals) need to overcome to get to where they are needed in the body. It is highly likely that a number of MAPPs designated medicines could fall into this category and the information and insight generated by this consortium could be used to develop and validate biopharmaceutical formulations to deliver these novel drugs to their targets in a more expeditiously process. To date there is little from this project in the public domain, but the scope of the research could lead to significant breakthroughs in the delivery and targeting of these different molecular modalities.

The focus of **OrBiTo** (www.orbitoproject.eu) has been to understand the interaction between drug substance physical characteristics and *in-vivo* permeability properties, with the formulation and the prandial state to improve the predictability of *in silico* methods which is entirely aligned with this CMC ADAPT SMART topic. The OrBiTo project has set about delivering predictive *in vitro* tests that will enable assessment of formulation and process changes including scale up without fully understanding the root cause of any differences which is a key component of reducing uncertainty associated with accelerated development.

3.3 WORKSTREAM 3

Out of the 17 IMI projects evaluated in WS3, five have yielded early embryonic ideas potentially applicable to MAPPs that have not yet been tested (Euc2lid, IMIDIA, STEM BANCC, SUMMIT, and Translocation), seven generated some developed ideas with limited tested concepts (BTCure, U-Biopred, eTox, K4DD, MIP-DILI, OncoTrack, PREDECT), two produced moderately developed ideas and tested concepts (BioVacSafe, QUIC concept), and one yielded highly developed and well tested concepts ready to be used as MAPPs (Newmeds). Some of these projects are still ongoing and may produce MAPP-relevant outputs or more advanced and tested concepts by the time they are completed (BioVacSafe, BTCure, eTox, Euc2lid, K4DD, MIP-DILI, QUIC concept Stem BANCC, Translocation); these may need revisiting at a later time.

Twenty-four (24) outputs emerged from the non-clinical review, and of those six were disease specific, in a bid to improve disease knowledge and drug target and specificity. **DDMoRe**, **e-TOX** and **SAFE-T** are the leading examples, with details of the output listed in the Appendix below. In terms of non-clinical outputs that can be considered relevant and valuable in a MAPPs scenario are *in vivo* toxicology, drug target profiling and propositions, data cataloguing, analytical methods, and use of modelling and simulation approaches. This is particularly important when we consider the criteria for MAPPs, and the fact that disease transformative medicines will be considered, where there is a predictive probability to define, deliver and measure quantifiable outcomes. All eleven remaining non-clinical outputs were linked to early safety signalling using data mining / cataloguing / modelling approaches – such approaches can be valuable in being able to predict the safety profile of the drug, and therefore allow for an estimation of the risk benefit profile.

The **SAFE-T** project is indeed a good example. One of the objectives of Drug-Induced Liver Injury (DILI) WP3 of the SAFE-T consortium was to qualify one or a set of new biomarkers that could more reliably diagnose, predict the outcome, and classify Drug-Induced Liver Injury. Originally, and as highlighted by the EMA, the overall strategy for biomarker selection was ambitious with regard to the initial selection, further exploration, and final confirmation within a variety of clinical trials. However, given time constraints and the limited number of patients available within the project timeframe, the DILI-WP decided to investigate 16 new biomarkers selected largely from the first stage gate analysis in one subsequent analysis using all available datasets, to no longer separate an exploratory from a confirmatory phase, and initiate discussion with the regulators. As a result, both the FDA[5] and the EMA[6] issued a letter of support in July and in September 2016 respectively, to encourage further research towards the prospective validation of the candidate biomarkers. The consortium has suggested exploratory use of the biomarkers in further clinical development, which currently do not allow final conclusions with regard to potential utility of these biomarkers in clinical practice.

NEWMEDS was a schizophrenia-focused project has created some tools that may be applicable to a wider range of CNS and non-CNS conditions. These include DupCheck, a web-based tool to screen for duplicate patients in clinical trials within and across studies, sponsors and therapeutic area, Pharmacological Imaging and Pattern Recognition Toolbox for the analysis of brain images for a better classification in the context of drug development and a Clinical Significance Calculator for biomarkers of depression treatment outcome.

One completed project (**MARCAR**) was judged as not being MAPP-relevant, and unfortunately no information could be obtained from one project (**PharmaCog**).

[5] http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM517355.pdf
[6] http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/09/WC500213479.pdf

3.4 WORKSTREAM 4

The majority of the outputs identified (n=37) were linked to the clinical phase of drug development, with 24 of those specific to biomarker discovery/validation. The biomarkers in question overlapped diagnostic, predictive and drug response. Such biomarker development is considered to be valuable in terms of identifying suitable patients better and in terms of gaining an earlier insight into drug efficacy.

Most of the clinical specific outputs (including biomarkers) were disease specific, across ten different disease areas: antimicrobial, diabetes, oncology, Alzheimer's disease, Rheumatoid Arthritis, pain, asthma, Chronic Obstructive Pulmonary Disease (COPD), depression and schizophrenia. Although tested in a specific domain (depression and schizophrenia) via the **NEWMEDS** (www.newmeds-europe.com) project, DupCheck which is a simple tool that can help improve compliance, reduce risks of misattributed safety signals and improve efficacy signals in clinical trials, could be easily applicable to other disease areas. These outputs can be seen according to disease grouping (Appendix 6.6).

When considering the disease areas most likely to be appropriate for a MAPPs approach as per defined in the discussion paper on engagement criteria (Appendix 6.7), it is anticipated that the focus will be on disease transformative medicines targeting a well-defined patient population with a specific high unmet need, i.e. life threatening or severely debilitating conditions for which no treatment or no satisfactory treatment exists. This population will have to be identified to the extent possible based on objective and quantifiable medical and epidemiological information. The disease areas studied in IMI projects that are most likely to fall under this remit therefore are oncology and Alzheimer's disease.

That's not to say that there is no relevance in the other disease areas, especially in some specific patients subsets, e.g. those more severe and difficult to treat, and might be considered in an iterative and staggered development starting with an initial approval in a restricted severe patient population in which there is a positive benefit:risk profile outweighs the risk. Although disease specific projects, PROactive and U-Biopred, which recently completed have delivered tools that will benefit future research in COPD and severe asthma respectively. As part of **PROactive** (www.proactivecopd.com), two patients reported outcome (PRO) hybrid instruments combining a questionnaire and an activity monitor, were developed to capture experience of physical activity in COPD patients and support labelling claim: the D-PPAC for the daily assessment and the C-PPAC for use during clinical study visits. These two PROs should be qualified soon by EMA. U-Biopred (www.ubiopred.eu) has tackled the challenges involved in developing personalised medicines for asthma. More specifically, U-BIOPRED has gathered vast amounts of samples and data from severe asthma patients as well as healthy people from across Europe, in a bid to identify distinct types of the disease. In a cohort study, scientists analysed gene activity and levels of certain proteins and lipids in sputum samples from severe asthma patients. They were able to identify three distinct patient clusters, which is the first step towards being able to provide each sufferer with optimal individualised treatment**,** the ultimate goal of personalised medicine. Results in children are still pending.

To achieve progressive reduction of uncertainty around efficacy and safety and/or to broaden the treatment-eligible population (e.g. from severe to moderate/mild), a prospective and realistic plan to conduct patient data collection and analysis post licensing is required. So far, **PROTECT** (www.imi-protect.eu) has contributed most in this area. Some of the outputs generated to date focus on methodological approaches, of which some can already be adopted and others enhanced further to be utilised in such contexts. The consortium issued some useful recommendations: guidance for observational studies[7], guidance for Good Signal Detection Practices which was used to update methods for signal detection from EudraVigilance[8], recommendations for B/R assessment methodologies and

[7] http://onlinelibrary.wiley.com/doi/10.1002/pds.v25.S1/issuetoc
[8] http://rd.springer.com/article/10.1007%2Fs40264-016-0405-1

visual representations based on real-world case examples to facilitate clear and transparent decision-making[9] or new methods to collect data directly from patients[10], including via the internet; this research included also the collection of information from pregnant women via the web to better understand the safety of medicines during pregnancy. Results are currently being implemented into routine pharmacovigilance and regulatory practice. They have already started to improve day-to-day medicines monitoring operations of regulators and pharmaceutical companies, for better safety of European patients. However, an area that needs further work, is applying methodologies that evaluate risk/benefit in diseases of high unmet needs i.e. life threatening or severely debilitating conditions for which no treatment or no satisfactory treatment exists, and to take patient's own perspectives into how and to which extent they consider uncertainty in risk and benefit.

Within the clinical biomarker outputs identified, there are certainly options that could be considered in terms of defining population cohorts with diagnostic biomarkers of various phenotypes, and utilising monitoring biomarkers to evaluate initial drug response which might then predict clinical benefit. All of the biomarkers developed within the selected IMI projects have focussed on a specific disease. It is therefore highly unlikely that any of the markers discovered may be applicable to other diseases. However, learning from the process to identify these may be applicable to other diseases, and may benefit MAPPs.

In addition to **U-Biopred** detailed above and where biomarkers have been developed to help phenotyping severe asthmatic patients, another interesting project is **EU-AIMS** (www.eu-aims.eu). As a result of their research, the EU-AIMS consortium has received a letter of support[11] from the EMA to investigate further a stratification tool, Eye-tracking methodologies, that could optimise clinical research in Autism Spectrum Disorder. **BT-Cure** (www.btcure.eu) is another similar project that has the potential to offer value in Rheumatoid Arthritis (RA). With this project, the consortium aim is to develop an understanding of the early process in arthritis subsets to enable the development of precise and eventually curative treatments to be used before irreversible destruction and loss of joint function and mobility have occurred in patients. The consortium has recently shown that very different genetic, environmental and thus molecular events are needed to trigger different subsets of the disease. The BTCure project will be followed up as it is expected to develop new diagnostic methods to discover the early forms of RA and RA-like diseases and new tools to differentiate the different forms of RA and RA-like diseases, where different molecular mechanisms are involved and where different therapies may be required; gene expression analysis may help defining personalised medicines. To achieve these goals, samples from biobanks will be analysed *in vitro* and animal models are expected to be developed using similar molecular pathways as the relevant human arthritis subsets. This should help better understand the aetiology and early pathophysiology of the disease and should thus help optimise future drug development targeting RA and RA-like disease patient population.

IMIDIA, **SUMMIT** and **DIRECT** have formally created an IMI diabetes platform to overcome key bottlenecks for novel therapies and improved diabetes management. **IMIDIA** (www.imidia.org) is working on the generation of novel biomarkers for diagnosis and prognosis of pancreatic beta-cell failure and for monitoring diabetes progression and success of disease treatment. IMIDIA has specifically looked at plasma lipids from the ceramide family as potential biomarkers for detection of future type 2 diabetes patients in the pre-diabetic phase based on two independent large cohorts. The study has been completed successfully but results have not yet been released. Several studies on the IMIDIA website report associations of gene variants with presence of obesity and/or type 2 diabetes, but none of them has been validated as enrichment marker or similar in confirmation cohort. **SUMMIT** (www.imi-summit.org) is expected to deliver a set of markers able to better

[9] http://onlinelibrary.wiley.com/doi/10.1002/pds.3958/abstract
[10] http://publichealth.jmir.org/2015/2/e22/
[11] http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/12/WC500198349.pdf

predict disease progression and drug effects thereby shorten clinical trials. An ultrasound/radiofrequency-based virtual histology for non-invasive assessment of plaque structure has been developed and passed through the final validation with good results. SUMMIT has completed the largest-ever GWAS for a number of major diabetes complications and generated almost all the data for the first-ever exome sequencing study of Diabetic Nephropathy. Independent genetic and soluble markers for cardiovascular complications have been identified, which levels suggest a novel pathway for CVD in type 2 diabetes and are now taken to the replication phase. However, much of the specifics of these successes remain to be disclosed. In addition, 10 animal models of human disease have been characterised. **DIRECT** (www.direct-diabetes.org) is also highly relevant to the MAPPs agenda, in terms of its focus on personalised medicines and stratification of patients with, or at risk of, type 2 diabetes. Its aim is to use biomarkers to predict those who will deteriorate rapidly, or those who will respond to therapy. The 2-year extension of the project is to allow for the validation of biomarkers for stratification in prospective studies.

AETiONOMY (www.aetoniomy.eu) seems to be an ambitious and promising project looking at organising mechanistic knowledge about neurodegenerative diseases (Alzheimer's and Parkinson's disease) for the optimisation of drug development and therapy, thus increasing patients' chances of receiving a targeted treatment that works for them. In contrast to the established disease classification systems e.g. the International Classification of Disease, the "mechanism-based taxonomy" will be based on the knowledge of the biological pathways involved in the aetiology of the disease leading to a classification of disease classes and subclasses. Again, as this is likely to be a disease area would fir the engagement criteria, this IMI project could yield useful tools.

DDMORE (www.ddmore.eu) has created a repository to improve quality, efficiency and cost effectiveness of Model-Informed Drug Discovery and Development (MID3) and therapeutic use. DDMoRe could potentially provide an important contribution to MAPPs as it could enable and facilitate greater use and understanding of the models available to be used to support an initial approval or subsequent expansion of the product label. Overall DDMoRe and the work of the EFPIA MID3 Work Group have achieved a great deal in providing better access and understanding of the usefulness of modelling for internal company decision-making, and in facilitating regulatory review. For MAPPs, however, a focus on the models available in the repository would be required in terms of identifying those which have the potential to be pivotal to the initial and life cycle benefit risk decision making; and ensuring there is an adequate level of understanding and confidence in those models by all stakeholders. For an appropriate use of the model, technical certification provided by the consortium would certainly need to be complemented by regulators' qualification.

EHR4CR (www.ehr4cr.eu) has built a platform to enable the use of EHR (Electronic Health Records) for more efficient medical research and run pilots (on interoperability, security, data quality, data storage solutions, organisational issues, accreditation and certification, etc) to demonstrate the viability and scalability of an EHR4CR business model. This project has been extensively analysed by CASMI in their report (IMIPACT final report, March 2015) which highlighted '*the potential value of EHR4CR in the MAPPs scenario is two-fold. First, early identification of specific patient groups and secondly, real-world data capturing opportunities for monitoring purposes (safety and effectiveness) using synchronized records*'. The report also raised a valid point on the need to *pre-agree standards and definition of the quality and quantity of data to be captured (and resolution of data safety and privacy issues) to ensure widespread utilisation and impact*. This project has applicability to workstream 4 and 5.

3.5 WORKSTREAM 5

In terms of outputs that are linked to Real World Data (RWD), and valuable to facilitate patient access to safe and effective medicines a total of 13 potential outputs were identified. Many of the outputs identified here are linked to generating a better understanding of the

adverse event profile and linked methodology to facilitate and improve the benefit:risk evaluation in the real-world setting.

In this regard, **PROTECT** is a mature project that offers innovative methods to improve and strengthen the monitoring of the benefits and risks of medicines marketed in the EU. PROTECT concentrated on:

- improving early and proactive signal detection,
- establishing a framework for pharmacoepidemiology studies,
- developing methods for continuous benefit-risk monitoring of medicines
- and enhancing data collection directly from consumers/patients.

Other projects besides **PROTECT** that have already been referred to under Workstream 4, but which also applies to RWD are **DIRECT, SUMMIT** and **PROactive**.

If we consider antibodies to biologics as a specific adverse event, **ABIRISK** (www.abirisk.eu) also has the potential to offer value as it intends to provide a new centralised database to capture reports of this type of adverse events, however there is no new output for evaluation of risk/benefit and no output concerning the infrastructure of process of assessment.

These are all aspects that are likely to be of great importance in a MAPPs context, and utilising such frameworks and methodologies important across all therapeutic areas.

As a disease-specific example which is likely to meet the engagement criteria for MAPPs, the **EMIF** platform (www.emif.eu) for Alzheimer's disease provides a promising example. It is intended to validate biomarkers and support the definition of extreme phenotype. The project aims to be a proof-of-concept as to whether biomarkers will facilitate trial design.

The main contribution linked to RWD, which is mature enough to be applicable now is provided by the **GET REAL** project (www.imi-getreal.eu) which looked at incorporating real world evidence into drug development prior to market authorisation – i.e. before classic observational research techniques can be applied to the drug on the market. Main outputs are 1) technical feasibility and stakeholder acceptance when combining observational and randomised clinical trials (RCTs); 2) understanding the drivers of the gap between efficacy and effectiveness, 3) exploring trial design options beyond RCTs, e.g. advancing operational aspects of pragmatic trials and 4) combining RWD and RCT data in different analytical approaches. Robust new methods of RWE collection and synthesis should be developed and considered for adoption earlier in pharmaceutical R&D and the healthcare decision making process. As part of this project, guidance on the optimisation and feasibility of pragmatic trials have been provided, and PragMagic, a decision support tool to help researchers design pragmatic trials is being developed and should be ready for use in Q1-2017. Novel therapies need to be evaluated in normal clinical practice to allow a true representation of the treatment effectiveness in real-world settings, hence the interest in pragmatic trials which implementation challenges need to be addressed. Two pragmatic trials which the project used as a basis for their discussion, recently delivered: the Salford Lung Study (Woodcock et al. 2015[12]; Vestbo et al. 2016[13]) and the SCOT study[14] (Standard care versus Celecoxib Outcome Trial). The Salford Lung Study has investigated the use of a new inhaler for COPD against the standard of care. An important feature of the study is the linkage to electronic health records (EHRs) for outcome measurements. With this study involving more than 2900 COPD patients, it has been shown that a once-daily treatment regimen of combined fluticasone furoate and vilanterol was associated with a lower rate of exacerbations than

[12] http://bmcpulmmed.biomedcentral.com/articles/10.1186/s12890-015-0150-8
[13] http://www.nejm.org/doi/pdf/10.1056/NEJMoa1608033
[14] McDonald et al, 2016:
http://eurheartj.oxfordjournals.org/content/ehj/early/2016/10/02/eurheartj.ehw387.full.pdf

usual care, without a greater risk of serious adverse events. It is important to point out that prior to finalising their study protocol, the Salford Lung Study team sought guidance on the study design under the joint scientific advice process from NICE and the MHRA. The SCOT trial was a post-launch pragmatic trial featuring a broad inclusion via GPs, aiming at wide generalizability and using EHRs as a source for outcome information. SCOT was set up to examine the comparative safety of treating arthritis either with commonly used non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, diclofenac and naproxen, or a newer class of more targeted drugs called COX2 inhibitors, which include celecoxib. This large-scale international study of more than 7000 arthritis patients with no history of heart attack or stroke, has found the risks arising from prescribed use of some of the most common pain killers are relatively low, offering reassurance to doctors and patients.

The learning's and methodologies learned here can be applied in future MAPPs products.

3.6 Grouping of outputs

Grouping of outputs per WS review, disease areas, and according to the traditional development paradigm is provided in appendix (Appendix 6.5 and 6.6, respectively). It shows that for most of the projects, tools and methods under development are disease specific and not applicable to other diseases.

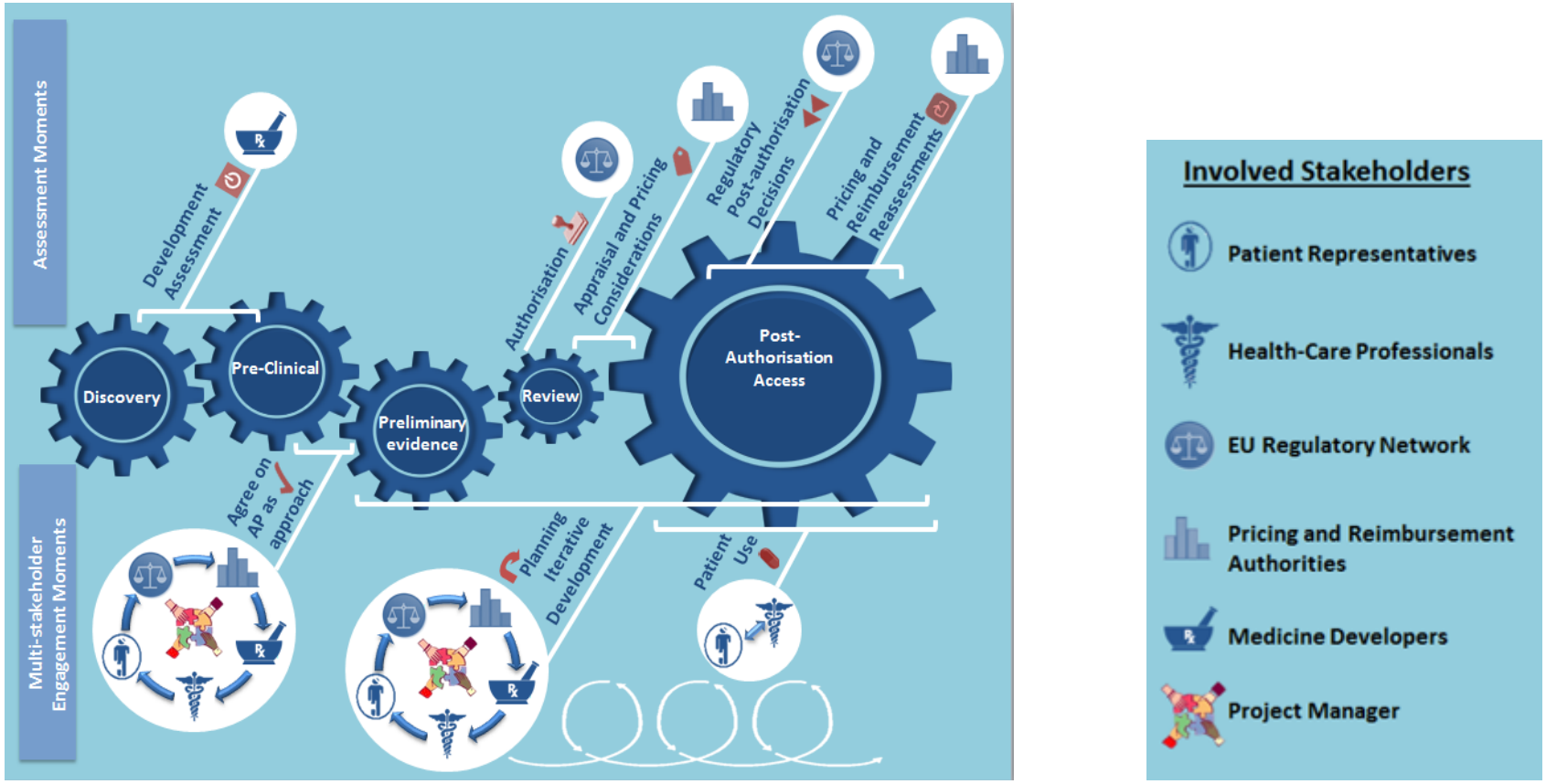
3.7 Place in the MAPPs Pathway

With MAPPs, it is expected to move away from a traditional drug development paradigm to a new iterative MAPPs adaptive pathway (Figure 3), where innovative tools and methods such as the identification of a target population via specific biomarkers, the used of innovative study designs or PROs, with incorporation of RWE from outset.

With Figure 3, the core moments of an adaptive pathway are illustrated. 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. Within the bottom portion of the diagram, moments of multi-stakeholder engagement are illustrated.

Figure 3: MAPPs Seamless Pathway and Decision Points

(Joint Draft Report of D2.05 and D3.02 deliverables – Aug. 2016)



4 Discussion

4.1 Strengths and limitations

We used a methodology that was modified from a previous initiative conducted prior to this review work, and which will be further refined when the review moves on to focus on EU non-IMI projects of interest. Collaborative work has involved diverse and complementary expertise provided by the consortium. Having so many different people review the work separately inevitably means that there will be some bias, and differences of interpretation in the findings which may account for some anomalies. This will occur despite providing guidance in the assessment template and organising ad hoc discussions to verify views.

Public and private consortium partners have been equally involved in the review, as well as in the analysis of the findings. This should ensure that both perspectives have been considered in the evaluation.

A workshop has been planned to discuss and finalise the conclusions of the review, which will pave the way for further review of IMI and non-IMI projects since further analysis and updates will be forthcoming at later dates in 2017, and according to WP1 workplan.

4.2 Gap analysis

Many IMI outputs have been identified that could contribute the MAPPs agenda, although most of them would require some further work and/or modification in order to be fully implemented in drug development. It must be remembered that none of the IMI projects (with the exception possibly of GetReal) were commissioned with MAPPs in mind, and therefore applying outputs generated for other objectives is likely to require some form of 'reverse engineering'. That is to say that the design and objectives of the IMI projects leading to the developments of the outputs identified did not consider MAPPs at that time, and any relevant needs and implications in this new context might need to be adjusted for.

In terms of the CMC/ Quality gaps the EFPIA TDEG is currently assessing potential opportunities for delivering reduced pharmaceutical development times (some of which are already being considered / addressed in the IMI projects OrBiTO and COMPACT).

Pre-clinical tools developed to date through IMI projects have provided a strong portfolio of tools and methodologies that can be used and tested for enhancing the MAPPs pathways, e.g. the development of animal models that could be recognised as contributory evidence when developing new therapies for asthma, Rheumatoid Arthritis, Alzheimer Disease or diabetic polyneuropathy are good examples. However, for most of the projects though, further work is needed to get full acceptance of those models e.g. via regulatory qualification. And, again, applying these to disease areas of relevance to MAPPs would need further consideration.

More can be done to also use increasing acceptance and use of extrapolation and modelling and simulation, which can enable the prediction of benefit/risk in different disease severity early on. Studies would therefore be prospectively planned to confirm predictions from modelling and/or extrapolation approaches. The DDMoRE project which has established a Model repository would probably need to consider model qualification to give more value to their repository.

Identification of innovative clinical trial methodologies, using small population statistics illustrating how MAPPs could be applied are generally missing from IMI work done to date however (bar a couple of exceptions where clinical trial designs and stratification of patients were explored in RA, Asthma and Autism). This work might emerge from GetReal as their work packages exploring trial design options beyond RCTs, e.g. advancing operational

aspects of pragmatic trials and combining RWD and RCT data in different analytical approaches.

Further work on trial methodologies which included population identification in specific disease areas of high unmet needs i.e. life threatening or severely debilitating conditions for which no treatment or no satisfactory treatment exists would also be a strong addition. This includes a statistical iterative / adaptive design where biomarker indication in the first iteration leads to evaluation of a clinical outcome in the second iteration. Evidence analysis and synthesis for these studies need cross-stakeholder agreement and buy-in early on.

Furthermore, applying methodologies that evaluate risk/ benefit in these diseases of high unmet needs and incorporating patients' own views and perspectives into how they consider uncertainty, risk and benefit is required. Taking on board these patients perspectives across the different diseases and across different disease severity is important for considering study designs and iterations. Future IMI2 projects may be informative in this respect.

Qualified biomarker availability in the diseases that are most likely to be considered for MAPPs would facilitate a MAPPs approach greatly and lead to greater acceptance by all stakeholder groups. As previously discussed, the diseases and therapeutic areas that have been the primary focus of IMI biomarker development to date has great insight into the process of biomarker development and validation, however these specific ones might not lend themselves specifically to MAPPs unless a specific drug with a specific mechanism of action could be identified in an area of high unmet therapeutic need.

That's not to say that IMI should fund biomarker development in each of the high-unmet diseases areas likely to be considered for MAPPs, but given that the IMI network now has a wealth of skills and expertise in biomarker development and qualification, with numerous biomarkers developed to date, this knowledge base should, as a priority, be captured, documented and disseminated to make the path from biomarker discovery to biomarker validation and qualification easier to navigate for others. This should include biomarker classification, but also needs to integrate the views of various stakeholder groups on what is considered to be a valid/ qualified biomarker, how this differs across different stakeholder groups and especially how that biomarker needs to correlate to real world outcomes that are of clinical relevance.

New tested methodologies and clearer guidelines on the acceptance and the type of RWE to be considered acceptable by all stakeholder groups is still lacking, including patient data input using mHealth / wearables for example. A mobile app for medicines safety monitoring was launched by the UK MHRA via WEB-RADR. PROTECT explored this in one small project focused on pregnant women use of medications however, this was generally rather limited in scope. Improving and enhancing data collection directly from patients (and consumers) do not go far enough to make the most of technology capabilities and possibilities today. IMI projects which have not yet delivered will be key to follow. WEB-RADR is one of those, where researchers are working together to detect new drug side effects by mining publicly available web and social media content. Another example, the EHR4CR project should provide adaptable, reusable and scalable solutions (tools and services) for reusing data from Electronic Health Record systems for Clinical Research, which offers large opportunities for the advancement of medical research, the improvement of healthcare, and the enhancement of patient safety. Understanding of regulatory needs, governance demands or requirements (through guidance and instructions) along with seeking the views of the patients in terms of being engaged/ empowered to be involved in the data generation while maintaining data privacy is necessary to move the capabilities and value of remote patient monitoring forward. Data standards and interoperability (incl. quality/ quantity control issues) are required in these fields, keeping in mind the practical issues of data generation within and outside the traditional clinical trial model.

Digital health is a topic of interest for the recent IMI call, and new methods and case studies are likely to emerge. However, given the time scale that it can take to implement a

completed study and demonstrate scientific evidence, a piece of work that can be implemented sooner would be to focus on usability, and clearer regulatory guidance on data requirements, quality and analysis.

5 Recommendations and Conclusions

This was the first round in a planned iterative process to contribute to increased learning and a better understanding that will allow for a refined methodology as the work continues.

This first review has identified a few outputs from IMI projects completed to date that can be considered relevant and useful to a MAPPs scenario. That usefulness can only be truly judged however in the eventual scenario that a drug/ molecule is identified as being considered suitable for a disease of high unmet need and fulfilling MAPPs pathway engagement criteria. In such a scenario, the biomarkers, tools and methodologies identified here can be implemented and tested in that scenario.

As mentioned previously however, this exercise relies on 'reverse-engineering', of identifying outputs developed for other outcomes and applying them to MAPPs. Using such 'adopted' outputs in a MAPPs approach therefore would still require either some modification and/or additional testing.

More work will be done to complete this initial review and help forming appropriate recommendations along these bases in subsequent reviews.

6 Appendices

6.1 IMI projects considered in the selection review

Acronyms	Titles
EMTRAIN	European Medicines Research Training Network
eTOX	Expert Systems for In Silico Toxicity Prediction
EU2P	Pharmacovigilance Training Programme
EUROPAIN	Pain Research
IMIDIA	Islet Cell Research
MARCAR	Non-Genotoxic Carcinogenesis
NEWMEDS	New Tools for the Development of Novel Therapies in Psychiatric Disorders
PHARMA-COG	Neurodegenerative Disorders
PharmaTrain	Pharmaceutical Medicine Training Programme
PRO- Active	COPD Patient Reported Outcomes
PROTECT	Strengthening the Monitoring of Benefit/Risk
SAFE-T	Qualification Of Translational Safety Biomarkers
SafeSciMET	Safety Sciences for Medicines Training Programme
SUMMIT	Surrogate Markers For Vascular Endpoints
U-BIOPRED	Understanding Severe Asthma
BTCURE	Inflammation – Translational Research
DDMoRe	Knowledge Management – Drug/Disease Modelling
EHR4CR	Knowledge Management – Electronic Health Records (EHR)
OncoTrack	Oncology – Molecular Biomarkers
Open PHACTS	Knowledge Management – Open Pharmacological Space
PREDECT	Oncology – Target Validation
QUIC-CONCEPT	Oncology – Imaging Biomarkers
RAPP-ID	Infectious Diseases – Diagnostic Tools
ABIRISK	Immunogenicity: Assessing The Clinical Relevance And Risk Minimization Of Antibodies To Biopharmaceuticals
BioVacSafe	Immunosafety Of Vaccines – New Biomarkers Associated With Adverse Events (Early Inflammation, Autoimmune Diseases And Allergy)
DIRECT	Development Of Personalized Medicine Approaches In Diabetes
EU-AIMS	Translational Endpoints In Autism
EUPATI	Fostering Patient Awareness On Pharmaceutical Innovation
MIP-DILI	Improving The Early Prediction Of Drug Induced Liver Injury In Man
PreDiCT-TB	Improving The Preclinical Models And Tools For Tuberculosis Medicines Research
CHEM21	Sustainable Chemistry – Delivering Medicines For The 21st Century
Compact	Delivery And Targeting Mechanisms For Biological Macromolecules
EMIF	A European Medical Information Framework (EMIF) Of Patient-Level Data To Support A Wide Range Of Medical Research - Information Framework / Knowledge Management Service Layer
eTRIKS	European Translational Information & Knowledge Management Services
K4DD	Understanding And Optimising Binding Kinetics In Drug Discovery
OrBiTo	In Vivo Predictive Biopharmaceutics Tools For Oral Drug Delivery
StemBANCC	Human Induced Pluripotent Stem (HIPS) Cells For Drug Discovery And Safety Assessment
EUC²LID	European Lead Factory – European Screening Centre
COMBACTE	ND4BB Topic 1: Innovative Trial Design & Clinical Drug Development - Subtopic 1B
Translocation	ND4BB Topic 2: Learning From Success And Failure & Getting Drugs Into Bad Bugs
ADVANCE	Developing A Framework For Rapid Assessment Of Vaccination Benefit/Risk In Europe
GetReal	Incorporating Real-Life Clinical Data Into Drug Development

Acronyms	Titles
AETIONOMY	Developing An Aetiology-Based Taxonomy Of Human Disease - Approaches to Develop a New Classification for Neurodegenerative Disorders
EBiSC	European Induced Pluripotent Stem Cell Bank
ENABLE	ND4BB Topic 3: Discovery And Development Of New Drugs Combatting Gram – Negative Infections - Subtopic 3A: Management and Resource Hub
PRECISESADS	Developing An Aetiology-Based Taxonomy Of Human Disease - Approaches to Develop a New Classification for Systemic Lupus Erythematosus (SLE) and Related Connective Tissue Disorders and Rheumatoid Arthr
COMBACTE-CARE	ND4BB Topic 5: Clinical Development Of Antibacterial Agents For Gram-Negative Antibiotic Resistant Pathogens
DRIVE-AB	ND4BB Topic 4: Driving Re-Investment In R&D And Responsible Use Of Antibiotics
SPRINTT	Developing Innovative Therapeutic Interventions Against Physical Frailty And Sarcopenia (ITI-PF&S) As A Prototype Geriatric Indication
WEB-RADR	WEBAE - Leveraging Emerging Technology For Pharmacovigilance
FLUCOP	Immunological Assay Standardisation And Development For Use In Assessments Of Correlates Of Protection For Influenza Vaccines
CANCER-ID	Blood-Based Biomarker Assays For Personalised Tumour Therapy: Value Of Latest Circulating Biomarkers
COMBACTE-MAGNET	ND4BB Topic 6: Epidemiology Research And Development Of Novel Systemic Antibacterial Molecules Against Healthcare-Associated Infections Due To Clinically Challenging Gram-Negative Pathogens - Subtopic
EPAD	European Platform To Facilitate Proof Of Concept For Prevention In Alzheimer's Disease (EPOC-AD)
iPiE	Intelligent Assessment of Pharmaceuticals in the Environment Eco-risk prediction (ERP)
ULTRA-DD	Generation Of Research Tools To Enable The Translation Of Genomic Discoveries Into Drug Discovery Projects
ZAPI	Zoonoses Anticipation And Preparedness Initiative (ZAPI)
APPROACH	Applied Public-Private Research enabling OsteoArthritis Clinical Headway
iABC Programme	ND4BB Topic 7

6.2 Selection matrix

Project acronym	Full name		Likely level of impact of the project output to MAPPs including other regulatory opportunities, stratified/ personalised medicine						Stage of project / timepoint relevant to review No2				Other Criteria					Final Total Score (Sum of scores)	Action			
				Relevant to workstream?															✓	🕘	✘	
			Yes=2 No=0	Early Life-Cycle Yes=1 No=0	CMC Yes=1 No=0	Evidence generation during clinical phase Yes=1 No=0	Evidence generation in real-world settings Yes=1 No=0	Impact on MAPPs Score (0-5)	Cell No.	Mature? Y/N	Part addresses MAPPs agenda?	Does the project have any outputs ready for analysis Yes=1 No=0	Themes or Areas	Disease specific Yes=1 No=0	If yes, transferable to other disease areas? Yes=1 No=0	Horizontal topics linked to MAPPs? Yes=1 No=0	Other Criteria Score					
AETIONOMY	AETIONOMY	Organising mechanistic knowledge about neurodegenerative diseases for the improvement of drug development and therapy	3	0	0	1	1	5	8	N	Y	1	AD/PD	1	1	0	2	8	1			1: Better taxonomy can lead to systematic disease understanding and better design i
APPROACH	APPROACH	Applied Public-Private Research enabling OsteoArthritis Clinical Headway	3	1	0	1	1	6	11	N	Y	0	Osteoarthrosis	1	0	0	1	7		1		1: Stratification methods that identifies different osteoarthritis phenotypes can be us
BioVacSafe	BioVacSafe	Biomarkers for Enhanced Vaccine Immunosafety	3	1	0	1	1	6	3	Y	Y	1	Vaccine biomarkers	0	0	1	1	8	1			1: Linked to safety profile of vaccines and not necessarily on their effectiveness. Early
BTCure	BTCure	Be The Cure	3	1	0	1	1	6	2	Y	Y	1	Rheumatoid Arthritis (RA	1	1	0	2	9	1			4: Suitable for methods used in early life-cycle (1) 1: Several WPs that range from exploring more precise diagnosis of RA and incorpora
CANCER-ID	CANCER-ID	Blood-Based Biomarker Assays For Personalised Tumour Therapy: Value Of Latest Circulating Biomarkers	3	1	0	1	1	6	11	N	Y	0	Oncology	1	0	1	2	8		1		1: Biomarkers could accelerate further development earlier on in oncology.
CHEM21	CHEM21	Chemical manufacturing methods for the 21st century pharmaceutical industries	3/0	0	1/0	0	0	5	4	Y	Y	1	Chemical manufacturing	0	0	1/0	1	7				5: To make the drug development process more environmentally friendly (2) 1: Not relevant to MAPPs, related to manufacturing environmental efficency.
COMBACTE	COMBACTE	Combatting Bacterial Resistance in Europe	3	1	0	1	1	6	6	Y	Y	1	Bacterial Resistance	1	0	0	1	8	1			5: new CT designs - 4 1: New clinical trial designs in the field of antibiotics that could facilitate developmen
COMBACTE-CARE	COMBACTE-CARE	Combatting Bacterial Resistance in Europe - Carbapenem Resistance	3	1	0	1	1	6	9	N	Y	0	Antibiotics	1	0	0	1	7		1		1: Carbapenem biomarkers can be used both further on drug discovery and also clini
COMBACTE-MAGNET	COMBACTE-MAGNET	Combatting bacterial resistance in Europe - molecules against Gram negative infections	3	1	0	1	1	6	9	N	Y	0	Antibiotics	1	0	0	1	7		1		1: See other COMBACTE descriptions
COMPACT	COMPACT	Collaboration on the optimisation of macromolecular pharmaceutical access to cellular targets	3	1	1	0	0	5	4	Y	Y	1	Biopharmaceuticals	0	0	1	1	7	1			4: Suitable for CMC review 1: Agree with CMC review but molecular target optimisation could optimises non-clin
DDMoRe	DDMoRe	Drug Disease Model Resources	3	1	0	1	0	5	2	Y	Y	1	Model & Simulation	0	0	1	1	7	1			5: 3 1: Modelling and simulation standards can ease alignment in evidence modelling and
DIRECT	DIRECT	Diabetes research on patient stratification	3	1	0	1	0	5	3	N	Y	1	Diabetes	1	1	1	3	9	1			4: Suitable for evidence generation / R-W 1: Not sure we agree with the R-W comment, otherwise we would score it 1 in the RV
DRIVE-AB	DRIVE-AB	Driving re-investment in R&D and responsible antibiotic use	0	0	0	0	0	0	9	N	N	0	Antibiotics	1	0	0	1	1			1	1: Mostly linked to antibiotic use and societal impact.
EBISC	EBISC	European Bank for induced pluripotent Stem Cells	0	0	0	0	0	0	8	N	Y	0	Pluripotent Cell research	0	0	1	1	1			1	1: Cell research can provide opportunities in R&D but no direct impact in MAPPs.
EMIF-CR	EMIF-CR	Electronic Health Records Systems for Clinical Research	3	0	0	1	0	4	2	Y	Y	1	Electronic Health Records Systems For Clinical	0	0	0	0	5		1		1: Not exactly sure this would support RW evidence generation, very focused on the
ELF	ELF	European Lead Factory	0	0	0	0	0	0	5	Y	N	1	High Throughput Screening	0	0	1	1	2			1	4: To boost your activities in drug discovery 1: Optimised discovery could contribute to better and earlier identification of assets.
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	Alzeimers and	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	4: Suitable for evidence generation AND R-W

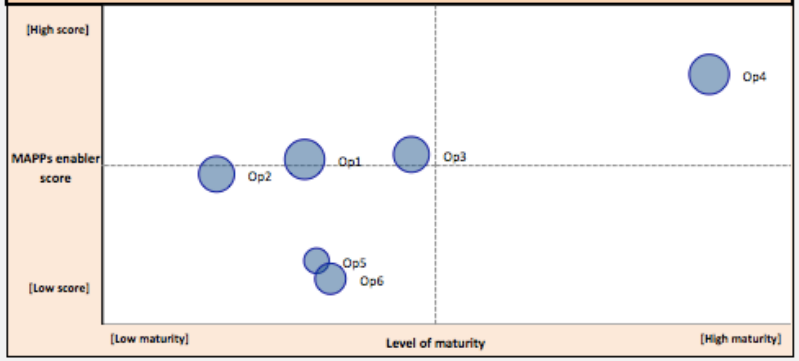
DIRECT

General informantion	
Project Name	Diabetes research on patient stratification
Call number	3
Disease focus area	Diabetes

Project participants	
EFPIA	4
SME's	0
Others	21
Total partners	**25**

Contributions €		
IMI Funding	€	21 400 000,00
EFPIA in kind	€	16 500 000,00
Other	€	5 200 000,00
Total cost	**€**	**43 100 000,00**

MAPPs related outputs graphic



Project Output/Outcome table

Output (Op) *Outcome*	Workstream relevance to MAPPs	Level of maturity	MAPPs enabler score
Op1: Biomarker discovery and validation *Disease stratification / personalised medicine*	2	5	3
Op2: Therapeutic response *Disease stratification / personalised medicine*	1	4	3
Op3: Glyceamic deterioration *Disease stratification / personalised medicine*	3	4	3
Op4: Data warehouse and biorepository *Knowledge data portal for research users (academic / industry)*	5	5	5
Op5: Assay development as a diagnostic *Disease stratification / personalised medicine*	2	2	1
Op6: Innovative trial design *Disease stratification / personalised medicine*	2	3	1

6.3 IMI Projects: outcome of initial evaluation by WS 1

Acronym	Topic Title	Workstream	Put on hold *	Rejected
ABIRISK	Immunogenicity: Assessing The Clinical Relevance And Risk Minimization Of Antibodies To Biopharmaceuticals	4 & 5	-	-
ADVANCE	Developing A Framework For Rapid Assessment Of Vaccination Benefit/Risk In Europe	-	5	-
AETIONOMY	Developing An Aetiology-Based Taxonomy Of Human Disease - Approaches to Develop a New Classification for Neurodegenerative Disorders	4	-	-
APPROACH	Applied Public-Private Research enabling OsteoArthritis Clinical Headway	-	4	-
BioVacSafe	Immunosafety Of Vaccines – New Biomarkers Associated With Adverse Events (Early Inflammation, Autoimmune Diseases And Allergy)	3 & 4	-	-
BTCURE	Inflammation – Translational Research	3 & 4	-	-
CANCER-ID	Blood-Based Biomarker Assays For Personalised Tumour Therapy: Value Of Latest Circulating Biomarkers	-	4	-
CHEM21	Sustainable Chemistry – Delivering Medicines For The 21st Century	-	-	x
COMBACTE	ND4BB Topic 1: Innovative Trial Design & Clinical Drug Development - Subtopic 1B	4	-	-
COMBACTE-CARE	ND4BB Topic 5: Clinical Development Of Antibacterial Agents For Gram-Negative Antibiotic Resistant Pathogens	-	4	-
COMBACTE-MAGNET	ND4BB Topic 6: Epidemiology Research And Development Of Novel Systemic Antibacterial Molecules Against Healthcare-Associated Infections Due To Clinically Challenging Gram-Negative Pathogens - Subtopic	-	4	-
COMPACT	Delivery And Targeting Mechanisms For Biological Macromolecules	2	-	-
DDMoRe	Knowledge Management – Drug/Disease Modelling	4	-	-
DIRECT	Development Of Personalized Medicine Approaches In Diabetes	4 & 5	-	-
DRIVE-AB	ND4BB Topic 4: Driving Re-Investment In R&D And Responsible Use Of Antibiotics	-	-	x
EBiSC	European Induced Pluripotent Stem Cell Bank	-	-	x
EHR4CR	Knowledge Management – Electronic Health Records (EHR)	-	-	x
ELF	European Lead Factory	-	-	x
EMIF	A European Medical Information Framework (EMIF) Of Patient-Level Data To Support A Wide Range Of Medical Research - Information Framework / Knowledge Management Service Layer	4 & 5	-	-
EMTRAIN	European Medicines Research Training Network	-	-	x
ENABLE	ND4BB Topic 3: Discovery And Development Of New Drugs Combatting Gram – Negative Infections - Subtopic 3A: Management and Resource Hub	-	4	-
EPAD	European Platform To Facilitate Proof Of Concept For Prevention In Alzheimer's Disease (EPOC-AD)	-	4	-
eTOX	Expert Systems for In Silico Toxicity Prediction	3	-	-
eTRIKS	ETRIKS - European Translational Information & Knowledge Management Services	-	-	x
EU2P	Pharmacovigilance Training Programme	-	-	x
EU-AIMS	Translational Endpoints In Autism	4	-	
EUC²LID	European Lead Factory – European Screening Centre	3	-	-

Acronym	Topic Title	Workstream	Put on hold *	Rejected
EUPATI	European Patients' Academy on Therapeutic Innovation	-	-	x
EUROPAIN	Pain Research	4	-	-
FLUCOP	Immunological Assay Standardisation And Development For Use In Assessments Of Correlates Of Protection For Influenza Vaccines	-	3	-
GetReal	Incorporating Real-Life Clinical Data Into Drug Development	4 & 5 (& WP3)	-	-
iABC Programme	ND4BB Topic 7	-	3 & 4	-
IMIDIA	Islet Cell Research	3	-	-
iPiE	Intelligent Assessment of Pharmaceuticals in the Environment - Eco-risk prediction (ERP)	-	-	x
K4DD	Understanding And Optimising Binding Kinetics In Drug Discovery	3	-	-
MARCAR	Non-Genotoxic Carcinogenesis	3	-	-
MIP-DILI	Improving The Early Prediction Of Drug Induced Liver Injury In Man	3	-	-
NEWMEDS	New Tools for the Development of Novel Therapies in Psychiatric Disorders	3-4	-	-
OncoTrack	Oncology – Molecular Biomarkers	3-4 & 5		
Open PHACTS	Knowledge Management – Open Pharmacological Space	-	-	x
OrBiTo	In Vivo Predictive Biopharmaceutics Tools For Oral Drug Delivery	2	-	-
PHARMA-COG	Neurodegenerative Disorders	3	-	-
PharmaTrain	Pharmaceutical Medicine Training Programme	-	-	x
PRECISESADS	Developing An Aetiology-Based Taxonomy Of Human Disease - Approaches to Develop a New Classification for Systemic Lupus Erythematosus (SLE) and Related Connective Tissue Disorders and Rheumatoid Arthr	-	3	-
PREDECT	Oncology – Target Validation	3		
PreDiCT-TB	Improving The Preclinical Models And Tools For Tuberculosis Medicines Research	-	3	-
PRO- Active	COPD Patient Reported Outcomes	4 & 5	-	-
PROTECT	Strengthening the Monitoring of Benefit/Risk	4 & 5	-	-
QUIC-CONCEPT	Oncology – Imaging Biomarkers	3 & 4	-	-
RAPP-ID	Infectious Diseases – Diagnostic Tools	4	-	-
SafeSciMET	Safety Sciences for Medicines Training Programme	-	-	x
SAFE-T	Qualification Of Translational Safety Biomarkers	4 & 5	-	-
SPRINTT	Developing Innovative Therapeutic Interventions Against Physical Frailty And Sarcopenia (ITI-PF&S) As A Prototype Geriatric Indication	-	4	-
StemBANCC	Human Induced Pluripotent Stem (HIPS) Cells For Drug Discovery And Safety Assessment	3	-	-
SUMMIT	Surrogate Markers For Vascular Endpoints	3-4 & 5	-	-
Translocation	ND4BB Topic 2: Learning From Success And Failure & Getting Drugs Into Bad Bugs	3	-	-
U-BIOPRED	Understanding Severe Asthma	3 & 4	-	-
ULTRA-DD	Generation Of Research Tools To Enable The Translation Of Genomic Discoveries Into Drug Discovery Projects	-	3	-
WEB-RADR	WEBAE - Leveraging Emerging Technology For Pharmacovigilance	-	-	x
ZAPI	Zoonoses Anticipation And Preparedness Initiative	-	-	x
TOTAL		**32**	**13**	**15**

*Projects put on hold for this review will be considered in a subsequent review when project outputs will be available.

6.4 Evaluation form used by WSs for the in-depth review of selected IMI projects

WP1 D1.02
Analysis of already completed and ongoing IMI projects

Please note that this form has to be completed by the workstream for which this IMI project is relevant

The review should be performed in the light of the D1.02 review process document

Analysis should be done using publicly available information, IMI project specific websites, publications, and information through personal dialogue with colleagues/project leader involved in the project

Date:

IMI project name:

Has this IMI project been completed? YESI__I NOI X I

If not completed, date of final completion:

Criterion score:
(As per total score identified by the initial screening workstream)

Workstream[15]: 2I__I 3I__I 4IXI 5I__I

It is requested that all selected IMI projects follow the same methodological review. This is to support the final analysis.
Please follow this approach as closely as possible.

[15] 2= CMC; 3= Tools/Methods used early in the life cycle; 4= clinical and HTA evidence generation; 5= Real world data collection.

1. Once your review of the project is complete, please score the project on the strength of evidence available using the following:

1= early embryonic ideas that have not yet been tested
2= some developed ideas with limited tested concepts
3= moderately developed ideas and tested concepts
4= developed and not fully tested concepts
5= highly developed and well tested/ready to be implemented concepts

1I__I 2I__I 3I X I 4I __I 5I__I

Comments:

Of note: considering that that different parts/work packages of the projects may have different levels of maturity, please specify if needed, which part of the project/work package is of interest. In the situation where there may be more than one part to consider, please add as needed.

1I__I 2I__I 3I__I 4IXI 5I__I

Comments:

2. Please summarise the output(s) identified that were considered relevant to MAPPs and provide explanation.

3. Please specify whether the output(s) can be considered disease specific and/or transferrable to other disease areas and/or wider use? (Please clearly specify YES/ NO / NOT SURE, and provide a 4-5 sentence MAX to explain your rationale for each one)

YES I__I NO I X I NOT SURE I__I (per output)

Comments:

4. Please score the importance of the findings as a MAPPs enabler from 1-4 using the following:

1= poor expected value/ contribution to MAPPs
2= some value/ contribution to MAPPs
3= moderate value/ contribution to MAPPs
4= important value/ contribution to MAPPs

1I__I 2I__I 3I X I 4I__ I

Comments:

5. Do you think that the project has not included certain areas of work or addressed certain questions or issues that you consider needed/relevant? If so, what are these areas of work which could warrant further work?

6. Please specify any other additional comments that has not been previously stated that you think is important

NB: all completed evaluations forms are available upon request.

6.5 Grouping of IMI project outputs by work streams

This grouping per Work Stream includes project outputs identified as a result of the review of the selected IMI projects. These outputs were then considered in the consolidated analyses for the purpose of this report.

WS2 CMC/quality

1. Enhanced use of biosynthetic processes for API manufacture (insight into the use of enzymes as catalysts).
2. Toolkits to evaluate new methodologies to streamline process development.
3. Biopharmaceutics computer based models and formulation and manufacturing process and use of in-silico tools, continuous manufacturing, use of modelling to facilitate scale-up and verification.
4. Biopharmaceutics Computer Based Models to understand the interaction between drug substance physical characteristics and *in-vivo* permeability properties.
5. Predictive in vitro tests to enable assessment of formulation and process changes including scale up without fully understanding the root cause of any differences.
6. Analysis on predictive tools used for oral drug absorption, published in scientific journals.
7. Database of the key properties of examples of over 80 oral drugs (with human PK data) as a source to enable oral drug absorption and human pharmacokinetic predictions to be tested and refined.
8. A systematic, multi-partner, bottom up, "blind prediction" of human pharmacokinetics using PBPK modelling completed on 43 of the database drugs.
9. An improved understanding of the human gastro-intestinal environment and behaviour (through techniques including regional intubation, electronic monitoring tablets, imaging and pharmacokinetic analysis).

WS3 non-clinical (pre-clinical)

1. The development of an animal model that could be recognized as contributory evidence when developing new therapies for asthma.
2. Establish predictive animal to humans' models in Rheumatoid Arthritis.
3. Identify new potential targets for AD drug development using genomics and proteomics approaches in presymptomatic and prodromal AD.
4. A new and more disease relevant animal model of diabetes polyneuropathy, the ZDF model, has now been further validated and compared to other models of diabetes polyneuropathy. The transgenic "knock-in" mouse strain of the NaV-channel SCN9a loci (K1449V and L858F mutations) show the expected phenotype
5. Four mouse models and one rat strain replicating diabetes vascular complications.
6. Three software tools for genetic markers discovery and prediction of diabetic complications.
7. Modelling approaches to drug binding kinetics has been published relative to Factor Xa inhibitors (Zhou et al., CPT: Pharmacometrics & Syst Pharmacol 4: 650-659, 2015).
8. Vitic Nexus eTOX database: 7139 preclinical reports cleared for sharing in the Vitic Nexus eTOX database, and of these 6647 reports have finished the extraction data process and are available;
9. eTOXlab available online: a flexible modelling framework developed for supporting models predicting the biological properties of chemical compounds (e.g. QSAR models)
10. LiMTox available online: a text mining approach that extracts associations between compounds and toxicological end points at various levels of granularity and evidence types
11. Collector available online: a tool that allows extracting from the Open PHACTS Discovery platform and the eTOX project series of compounds annotated with experimental data that can be used directly for building QSAR predictive models.

12. Standardiser available online: a tool designed to provide a simple way of standardising molecules as a prelude to e.g. molecular modelling exercises.
13. Verification tool available online: the verification of the models developed within the eTOX project comprises an assessment of (i) the quality of data used to build (and test) the model, (ii) whether the predictions generated by the model when executed in eTOXsys are consistent, and (iii) the completeness of the documentation accompanying the model.
14. During the eTOX extension phase (ENSO) a new task entitled "Linkage to human safety information" has been included.
15. Modelling approach intended to improve prediction of human DILI (drug induced liver injury) based on non-clinical data. (DILI article in Regulatory Toxicology and Pharmacology).
16. Generic Clinical Qualification Process for Translational Safety Biomarkers DIKI (drug induced kidney injury) BM qualification strategy: A consortium for the regulatory qualification of human kidney biomarkers to monitor drug-induced kidney injury DILI (drug induced liver injury) BM qualification strategy:
17. Model Repository is in the public domain since Dec 2015 (visit http://repository.ddmore.eu) Currently around 70 models uploaded covering a wide range of models used in MBDD/MID3 (Includes Model Description Language (MDL) published allowing to code models, components and associated workflow tasks / Model Coding System Standard developed (PharmML) to allow compute exchange of all modelling components / Beta-version of Modelling Framework (IDE) released in Dec 2015 implementing the user model execution interface / Model Certification Process initiated to facilitate independent qualification of Models stored in Repository and available to the public.
18. Model Repository is in the public domain since Dec 2015 (visit http://repository.ddmore.eu) with around 70 models uploaded covering a wide range of models used in MBDD/MID3
19. Model Description Language (MDL) published allowing to code models, components and associated workflow tasks
20. Model Coding System Standard developed (PharmML) to allow compute exchange of all modelling components
21. Beta-version of Modelling Framework (IDE) released in Dec 2015 implementing the user model execution interface
22. Model Certification Process initiated to faciliate independent qualification of Models stored in Repository and available to the public
23. Series of training courses conducted to introduce the DDMoRe framework concept, promote MID3 across a variety of disease areas, while targeting different stakeholders in industry and academia
24. In the process to create a successor organization to the IMI consortium, the DDMoRe Foundation, coming to life in Q3 2016

WS4 clinical

1. Develop new clinical trial criteria to find and recruit suitable RA patients in order to increase the relevance of clinical trial outcomes and, thus, the success of such trials
2. Investigate the reaction on interventional treatment against RA in subjects who are at significant risk of developing RA.
3. Diagnostic criteria and cut-offs on "gold-standard" clinical instruments for selection of patients with Autism Spectrum Disorders;
4. Clinical scales and cut-offs for each scale that represent clinically meaningful changes to evaluate outcomes after interventions in Autism. (Eye Tracking as a methodology to be used in autism research is of high importance for MAPPs due to its buy-in to investigate further a stratification tool that can optimise clinical research in the area. Such study can allow for new inclusion criteria and better defined patients that can hopefully allow for better efficacy detection earlier on).

5. Characterizing signs and symptoms of chronic pain in those patients who develop chronic pain after surgery. This includes predictive factors, validation of diagnosis specific tools for functional assessment as well as the impact of different surgical techniques and type of chemotherapy used on the incidence of chronic pain after surgery and adjunctive cancer treatment.
6. The placebo response (in pain) meta-analysis demonstrated that type of drug was the only factor significantly influencing the placebo response, opioid trials having a greater placebo response. Further studies on placebo and nocebo point to the importance of controlling for these effects in clinical trials in volunteers and in patients.
7. Results from an imaging study in healthy volunteers subjected to capsaicin injection and analgesics give sample size estimates for imaging endpoints useful in small proof of concept studies for drug development (in pain).
8. Two Patient Reported Outcome (PRO) instruments have been developed to be qualified and support labelling claim, in order to capture experience of physical activity in patients with Chronic Obstructive Pulmonary Disease (COPD): One for the daily assessment of physical activity: the D-PPAC with a one day recall period, and one for use during clinical study visits: the C-PPAC, with a 7 day recall period.
9. DupCheck: a simple tool that can help improving compliance, reduce risks of misattributed safety signals and improve efficacy signals in clinical trials (DEPRESSION AND SCHIZOPHRENIA).
10. Development of Care Test (POCT) Prototype Point, a platform for rapid detection of bacteria, mycobacteria (tuberculosis bacteria), fungi, as well as viruses in hospital patients in less than 2 hours and for outpatients in less than 30 minutes.
11. Determining resistance to the most commonly used antibiotics.
12. The ASPIRE-ICU study, to help understanding the epidemiology of AMR infection in order to address the potential infection "hubs" where the highest number of AMR infection is recorded, and to target the development of new antibiotic drugs in the centres that need it most without exposing patients that may not need them. This will be also a worthwhile strategy to reduce the appearance of resistance to new drugs, that is unavoidable is antibiotics are extensively used.
13. The COMBACTE CLIN-Net. This network of centres will be the basis for any clinical trials coming from the development of drugs from Pharma. It includes 28 centres so far.

Clinical biomarkers

1. Establish a personalized medicine approach to RA therapy through characterization and the development of peripheral blood biomarkers
2. EMA biomarker qualification advice for patient stratification. Improved knowledge may serve as a patient stratification tool in clinical development programs and to simplify personalized pain treatment.
3. Independent genetic and soluble markers for cardiovascular complications were identified and are now taken to the replication phase.
4. Four soluble biomarkers of diabetic retinopathy
5. Ultrasound/radiofrequency based virtual histology for non-invasive assessment of atherosclerotic plaque structure (a surrogate end point for hard cardiovascular end points).
6. SUMMIT completed the largest-ever GWAS (Genome-Wide Association) database for a number of major diabetes complications and generated almost all the data for the first-ever exome sequencing study of Diabetic Nephropathy. It has identified a genetic region that is associated both with CVD risk and biomarker levels suggesting a novel pathway for CVD in type 2 diabetes.
7. Data mining and in silico modelling in AD.
8. Platform/matrix of biomarkers (understood here mainly as a combination of cognitive tests, MRI and EEG data harmonized across the whole PharmaCog project) that may be sensitive to capture the impact of two cognitive challenge models (i.e. Sleep deprivation and transcranial magnetic stimulation) in AD.

9. Plasma lipidomic analysis to identify specific plasma lipids as potential biomarkers for detection of future type 2 diabetes patients in the pre-diabetic phase based on two independent large cohorts.
10. Provide new biomarkers or diagnostic methods to discover the early forms of RHEUMATOID ARTHRITIS (RA)
11. Provide new tools to separate the different form of RA, where different molecular mechanisms are involved and where different therapies may be required
12. Biomarkers to identify subtypes with rapid diabetes development and progression and altered response to diabetes treatments, and surrogate response biomarkers that reflect the underlying disease progression.
13. Potential biomarker(s) for fast 'progression' or drug response / non-response in T2D
14. EMIF-Platform, a large data repository of AD patient data to allow biomarker discovery studies within the EMIF; this will facilitate large-scale biomarker discovery and replication studies.
15. Discover and validate new biomarkers in plasma, cerebrospinal fluid and using MRI for the diagnosis and prognosis of AD in the presymptomatic and prodromal stage using the extreme phenotype approach.
16. Discovery of predictors of the metabolic complications of adult and paediatric obesity shall lead to innovative diagnostic tests, pave the way to novel therapeutics targeted to high-risk individuals, and provide the infrastructure to select individuals for such targeted pharmacological interventions.
17. EMIF-Metabolic aims to identify genetic causes of obesity and their relation to the metabolic complications of obesity. And characterize individuals and identify markers associated with metabolic risk irrespective of degree of obesity based on the knowledge that many obese individuals do not become dysmetabolic and insulin resistant.
18. Pharmacological Imaging and Pattern Recognition Toolbox for the analysis of brain images for a better classification in the context of drug development (DEPRESSION AND SCHIZOPHRENIA)
19. Clinical significance calculator for biomarkers of depression treatment outcome (www.depressiontools.org).
20. Clinical significance calculator: a simple tool to estimate whether a biomarker which predicts the outcome of depression treatment is likely to be clinically significant;
21. Four specific imaging biomarker validations in cancer have been published.
22. An imaging biomarker roadmap for evaluating imaging biomarkers in oncology (O'Connor et al. Nature Reviews clinical Oncology (in revision) 2016).
23. The creation of biobanks of adult and paediatric cohorts of severe asthmatics;
24. Clinical, physiological and omics biomarkers of severe asthma phenotypes.

WS 5 Real World Data

1. Data linkage from research cohorts to electronic health registry data and use to electronic health registry data to define extreme phenotypes.
2. The objectives of GetReal relate to incorporating real world evidence into drug development prior to market authorisation – i.e. before classic observational research techniques can be applied to the drug on the market. The methodologies being explored for technical feasibility and stakeholder acceptance all in some way combine observational and RCT research philosophies:
3. Understanding the drivers of the gap between efficacy and effectiveness,
4. Exploring trial design,
5. Advancing operational aspects of pragmatic trials and combining RWD and RCT data in different analytical approaches. All these would be relevant to assessing an evidence base consisting of results from a variety of research methods accumulating over time during adaptive development. The acceptability of different research options has been explored with HTA and Regulatory bodies; and the whole programme has demonstrated successful collaboration between stakeholders that could be built on to facilitate successful adaptive development strategies.

6. Innovative methods to improve and strengthen the monitoring of benefits and risks of medicines marketed in the EU through improving early and proactive signal detection,
7. Establishing a framework for pharmacoepidemiology studies,
8. Developing methods for continuous benefit-risk monitoring of medicines and
9. Enhancing data collection directly from consumers/patients.
10. Database on nationwide drug consumption in Europe, containing source information about ADRs, which facilitates the evaluation of drug exposure
11. Database of ADRs listed in the SPC of centrally authorized medicines
12. An exploratory study of self-reported medication use in pregnant women
13. Recommendations on methodological aspects related to multi-database studies conducted in several EU countries.

6.6 IMI Project grouping according to Disease grouping

Rheumatoid Arthritis (RA)

14. Develop new clinical trial criteria to find and recruit suitable RA patients in order to increase the relevance of clinical trial outcomes and, thus, the success of such trials
15. Investigate the reaction on interventional treatment against RA in subjects who are at significant risk of developing RA.

Autism

16. Diagnostic criteria and cut-offs on "gold-standard" clinical instruments for selection of patients with Autism Spectrum Disorders;
17. Clinical scales and cut-offs for each scale that represent clinically meaningful changes to evaluate outcomes after interventions in Autism. (Eye Tracking as a methodology to be used in autism research is of high importance for MAPPs due to its buy-in to investigate further a stratification tool that can optimise clinical research in the area. Such study can allow for new inclusion criteria and better defined patients that can hopefully allow for better efficacy detection earlier on).

Pain

18. Characterizing signs and symptoms of chronic pain in those patients who develop chronic pain after surgery. This includes predictive factors, validation of diagnosis specific tools for functional assessment as well as the impact of different surgical techniques and type of chemotherapy used on the incidence of chronic pain after surgery and adjunctive cancer treatment.
19. The placebo response (in pain) meta-analysis demonstrated that type of drug was the only factor significantly influencing the placebo response, opioid trials having a greater placebo response. Further studies on placebo and nocebo point to the importance of controlling for these effects in clinical trials in volunteers and in patients.
20. Results from an imaging study in healthy volunteers subjected to capsaicin injection and analgesics give sample size estimates for imaging endpoints useful in small proof of concept studies for drug development (in pain).

COPD

21. Two Patient Reported Outcome (PRO) instruments have been developed to be qualified and support labelling claim, in order to capture experience of physical activity (PA) in patients with Chronic Obstructive Pulmonary Disease (COPD): One for the daily assessment of physical activity: the D-PPAC with a one day recall period, and one for use during clinical study visits: the C-PPAC, with a 7 day recall period. To which extent this work could be used to assess PA in other chronic disease, such as RA?

TOOLS

22. DupCheck: a simple tool that can help improving compliance, reduce risks of misattributed safety signals and improve efficacy signals in clinical trials (DEPRESSION AND SCHIZOPHRENIA). Although tested in depression and schizophrenia, this tool could be used to spot duplicate **duplicate enrolment in trials. NOT DISEASE SPECIFIC**

Clinical biomarkers

RA

25. Establish a personalized medicine approach to RA therapy through characterization and the development of peripheral blood biomarkers

CV/diabetes

26. Independent genetic and soluble markers for cardiovascular complications were identified and are now taken to the replication phase.
27. Four soluble biomarkers of diabetic retinopathy
28. Ultrasound/radiofrequency based virtual histology for non-invasive assessment of atherosclerotic plaque structure (a surrogate end point for hard cardiovascular end points).
29. SUMMIT completed the largest-ever GWAS (Genome-Wide Association) database for a number of major diabetes complications and generated almost all the data for the first-ever exome sequencing study of Diabetic Nephropathy. It has identified a genetic region that is associated both with CVD risk and biomarker levels suggesting a novel pathway for CVD in type 2 diabetes.

Alzheimer Disease (AD)

30. Data mining and in silico modelling in AD.
31. Platform/matrix of biomarkers (understood here mainly as a combination of cognitive tests, MRI and EEG data harmonized across the whole PharmaCog project) that may be sensitive to capture the impact of two cognitive challenge models (i.e. Sleep deprivation and transcranial magnetic stimulation) in AD.

Type 2 Diabetes (T2D)

32. Plasma lipidomic analysis to identify specific plasma lipids as potential biomarkers for detection of future type 2 diabetes patients in the pre-diabetic phase based on two independent large cohorts.

Rheumatoid Arthritis (RA)

33. Provide new biomarkers or diagnostic methods to discover the early forms of RHEUMATOID ARTHRITIS (RA)
34. Provide new tools to separate the different form of RA, where different molecular mechanisms are involved and where different therapies may be required

DIABETES

35. Biomarkers to identify subtypes with rapid diabetes development and progression and altered response to diabetes treatments, and surrogate response biomarkers that reflect the underlying disease progression.
36. Potential biomarker(s) for fast 'progression' or drug response / non-response in T2D

AD

37. EMIF-Platform, a large data repository of AD patient data to allow biomarker discovery studies within the EMIF; this will facilitate large-scale biomarker discovery and replication studies.
38. Discover and validate new biomarkers in plasma, cerebrospinal fluid and using MRI for the diagnosis and prognosis of AD in the presymptomatic and prodromal stage using the extreme phenotype approach.

Metabolic disorders – at risk patients adults & paediatrics

39. Discovery of predictors of the metabolic complications of adult and paediatric obesity shall lead to innovative diagnostic tests, pave the way to novel therapeutics targeted

to high-risk individuals, and provide the infrastructure to select individuals for such targeted pharmacological interventions.

17. EMIF-Metabolic aims to identify genetic causes of obesity and their relation to the metabolic complications of obesity. And characterize individuals and identify markers associated with metabolic risk irrespective of degree of obesity based on the knowledge that many obese individuals do not become dysmetabolic and insulin resistant.

DEPRESSION

39. Pharmacological Imaging and Pattern Recognition Toolbox for the analysis of brain images for a better classification in the context of drug development (DEPRESSION AND SCHIZOPHRENIA)

18. Clinical significance calculator for biomarkers of depression treatment outcome (www.depressiontools.org).
19. Clinical significance calculator: a simple tool to estimate whether a biomarker which predicts the outcome of depression treatment is likely to be clinically significant;

ONCOLOGY

20. Four specific imaging biomarker validations in cancer have been published.
21. An imaging biomarker roadmap for evaluating imaging biomarkers in oncology (O'Connor et al. Nature Reviews clinical Oncology (in revision) 2016).

ASTHMA

22. The creation of biobanks of adult and paediatric cohorts of severe asthmatics;
23. Clinical, physiological and omics biomarkers of severe asthma phenotypes.

Anti infectives & ATB resistance

14. Development of Care Test (POCT) Prototype Point, a platform for rapid detection of bacteria, mycobacteria (tuberculosis bacteria), fungi, as well as viruses in hospital patients in less than 2 hours and for outpatients in less than 30 minutes.
15. Determining resistance to the most commonly used antibiotics.
16. The ASPIRE-ICU study, to help understanding the epidemiology of AMR infection in order to address the potential infection "hubs" where the highest number of AMR infection is recorded, and to target the development of new antibiotic drugs in the centres that need it most without exposing patients that may not need them. This will be also a worthwhile strategy to reduce the appearance of resistance to new drugs, that is unavoidable is antibiotics are extensively used.
17. The COMBACTE CLIN-Net. This network of centres will be the basis for any clinical trials coming from the development of drugs from Pharma. It includes 28 centres so far.

6.7 Discussion paper on engagement criteria

ADAPT SMART Work Package D2.03

Discussion paper on Engagement Criteria for MAPPs

http://adaptsmart.eu/wp-content/uploads/2016/02/ADAPT-SMART-Engagement-Criteria-Final1.pdf

Background on MAPPs and ADAPT SMART

Medicine Adaptive Pathways to Patients (MAPPs) is a widely discussed concept that "*seeks to foster access to [novel] beneficial treatments for the right patient groups at the earliest appropriate time in the product life-span, in a sustainable fashion.*"[16]

MAPPs seek to address the 'evidence versus access' conundrum faced by patients, physicians, healthcare decision makers and pharmaceutical innovators. For an in-depth description of this conundrum and of the principles and goals underpinning the MAPPs approach, please refer to the following articles and website [17] [18] [19] [20].

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

"*[MAPPs] foresee an initial marketing authorisation (MA) and reimbursement of a medicinal product in a well-defined patient subgroup and subsequent widening of the indication to a larger patient population based on additional evidence gathered and/or a conditional marketing authorisation and conditional reimbursement where initial data are confirmed [inter alia] through the collection of post-authorisation data on the medicinal product's use*[21]*."*

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

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

ADAPT SMART is a multi-stakeholder consortium that was set up as a *Coordination and Support Action* (CSA) under the EU Innovative Medicines Initiative 2 (IMI2).[22] The objective of ADAPT SMART is not to conduct primary research, but to establish an enabling platform and engage a dialogue with relevant stakeholders for the coordination of MAPPs-related activities. The consortium will conduct gap analysis, inform future research activities, and

[16] http://adaptsmart.eu/wp-content/uploads/2015/09/ProjectOverview-IMI2-ADAPTSMART.pdf
[17] Eichler et al. From adaptive licensing to adaptive pathways: delivering a flexible life span approach to bring new drugs to patients. Clin Pharmacol Ther. 2015 Mar;97(3):234-246
[18] Woodcock J. Evidence vs. access: can twenty-first-century drug regulation refine the tradeoffs? Clin Pharmacol Ther. 91:378-380 (2012)
[19] http://adaptsmart.eu/
[20] EMA reference on Adaptive pathway pilot: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp&mid=WC0b01ac05807d58ce
[21] ADAPT SMART Glossary http://adaptsmart.eu/wp-content/uploads/2016/04/D2-02-ADAPT-SMART-Glossary-first-edition.pdf
[22] http://www.imi.europa.eu/content/home

engage in knowledge management activities - all with a view to facilitate and accelerate the availability of MAPPs.[23]

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

Introduction to MAPPs selection criteria

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

Other facilitated pathways[24], for example the US FDA's 'Breakthrough Therapy Designation', have elaborated engagement criteria that could inform MAPPs, but these are focused on the regulatory part of the development and access. MAPPs are much broader, incorporating HTABs, payers, patients and prescribers and these key stakeholders may have additional or different requirements and/or preferences. Another factor to take into account is that re-imbursement/payment is a national matter in the EU which needs to be factored into the MAPPs discussion and increases the complexity.

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

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

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

Engagement criteria: a set of questions

Taking account of all stakeholders' perspectives on what types of products and clinical conditions would be eligible for MAPPs, it is important to address a set of key questions. These questions will trigger discussions initially at the company's level and subsequently at interaction meetings between the company and the other stakeholders. In turn, the responses to the questions that stakeholders come up with will drive the selection or de-selection of a product for MAPPs. For ease of reference, the questions are listed in Figure 1 and discussed in detail below.

[23] http://adaptsmart.eu/
[24] Baird et al, Accelerated Access to Innovative Medicines for Patients in Need, CPT 2014

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

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

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

The MAPPs focus should be on disease transformative medicines, targeting well-defined patient populations with a high unmet medical need, i.e. life threatening or severely debilitating conditions for which no treatment or no satisfactory treatment exist. Such populations will have to be identified, to the extent possible, based on objective and quantifiable medical information. Information on the disease's main features, including relevant epidemiological data, natural history, evolution with available treatment options or standard of care, and variations between countries or patients' populations will have to be addressed with reference to relevant guidelines, publications and/or registries. If relevant, the unmet medical need will be described separately for different subpopulations to select patients that could benefit best from the medicine[25].

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

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

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

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

Risk Management Plans (RMPs) are currently identifying key uncertainties around safety (and efficacy) aspects and include proposed actions for reducing those uncertainties[26]. A prospective and realistic plan for conducting clinical trials and/or collecting RWE post MA would need to be discussed and agreed upon as early as possible with all relevant stakeholders. Similar to what is expected with any standard current development practice,

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

an in-depth knowledge of the R&D environment and of the health care system(s) should be a pre-requisite to select a realistic plan.

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

In addition to study designs and analysis plans, the infrastructure required for data generation should be clearly and realistically defined and agreed upfront with all the stakeholders. This is to ensure (financially) sustainable pan-EU collection/analysis of post-MA data and may be based on existing disease registries, patient surveys, or access to adequate e-health records from insurance companies. Alternatively, stakeholders may agree on the creation of a *de novo* registry. An option could be a data collection system through a network of clinical 'centres of excellence' with functional capacities in terms of real-world data collection, management and sharing[27]. Setting up disease registries could be an area for early pre-competitive collaboration between stakeholders.

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

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

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

Disclosure of clinical trial data, regulators' public assessment reports, and approved product information will help providing adequate information on products' benefits and risks. In some instances, measures to ensure appropriate prescribing may be implemented by way of RMPs; these could be complemented with other tools and methods, such as drug utilisation studies and payer-initiated actions. (ADAPT SMART work package 2.7. will address this topic.)

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

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

The MAPPs concept relies on continuous knowledge generation and iterative assessment of

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

benefit-risk and value of a product. For a given MAPPs product it cannot be ruled out that after initial MA and reimbursement either the pre-agreed additional information/data/studies are not forthcoming, or that additional data do not support the earlier assumption of high patient benefit.

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

Multi-stakeholder interactions are of crucial importance when a MAPPs product is considered, for initial planning and to discuss appropriate corrective actions at key milestones during the product lifespan, depending on data read-outs. This could consist of the identification of key time points to align with various pre-agreed requirements and procedures; or to identify specific trigger points for decision-making (e.g. based on number of patients treated or studies completed); or what happens when the medicine gets to the prescribers and patients, e.g. are systems able to ensure only the appropriate patients get access, plans to ensure prescribers are adequately trained, or advice for patients/consent and monitoring to ensure patients are safe and can give feedback. Sufficient company, regulator, HTABs/payer resources need to be planned to allow stakeholders to interact appropriately. From a practical perspective, it is understood that initially only a limited number of MAPPs products could run in parallel. Capacity to ensure appropriate/timely stakeholder interaction is not a given and will depend on stakeholders' clear willingness at many time points to provide knowledge and capacity to generate and analyse comprehensive datasets.

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

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

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

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

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

Conclusion

Discussions among the ADAPT SMART consortium members have shown that universal MAPPs engagement criteria will likely be difficult to agree upon; this reflects the reality that different actors represent sometimes opposing interests and positions in the discussions. However, consortium members representing different stakeholder groups agreed that the questions listed and explained above will be relevant and would be considered when

selecting individual MAPPs products. The answers to these questions and, ultimately, the decision to select or de-select a specific product will depend on circumstances and can only be made on a case-by-case basis. Reaching a consensus among all stakeholders depend on their willingness to participate in the MAPPs process through appropriate and constructive discussions to allow the access to transformative products to patient with high unmet medical needs.

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