



Ethical And Legal Aspects Of Prescribing And Use By Target Populations

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Abbreviations

MAPPs	Medicines Adaptive Pathway to Patients
ADAPT-SMART	Accelerated Development of Appropriate Patient Therapies: a Sustainable, Multi-stakeholder Approach from Research to Treatment-outcomes
HCP	Health Care Professional
IMI	Innovative Medicines Initiative
MA	Marketing Authorization
MS	Member States
MAH	Market Authorisation Holder
HTA	Health Technology Assessment
DHPCs	Direct Healthcare Professional Communications
ERN	European Reference Networks
MS	Member States
RCT	Randomised controlled trial
RWE	Real World Evidence
SA	Scientific Advice
MAA	Managed Access Agreement
SmPc	Summary of Product Characteristics
P&R	Pricing and Reimbursement
GMC	General medical council
GMP	Good medical practice
GMPPD	Good medical practice professional development
PASS	Post Authorisation Safety Study
PAES	Post Authorisation Efficacy Study
CEE	Central and Eastern Europe
GDP	Gross Domestic Product

1. Executive Summary

Medicines Adaptive Pathways to Patients (MAPPs) is a widely discussed concept that foresees a more effective use of existing tools and building blocks to expedite patient access to beneficial treatments for the right patient groups at the earliest appropriate time in a sustainable fashion. For example, MAPPs foresees an initial marketing authorisation (MA) - either as a conditional MA (CMA) or a full MA in a well-defined but limited patient group and, utilizing the lifespan approach to continuous knowledge generation throughout the on-market use. Thus it aims to; (i) achieve rapid reduction of remaining uncertainties around efficacy and safety, (ii) allow for broadening (or contracting) of the treatment-eligible population where justified, and (iii) inform payers about use and effectiveness in order to enable flexible pricing and reimbursement schemes.

As part of an early assessment by the medicine developer, and later dialogues with other stakeholders as to the justification of using a MAPPs approach for product development, one of the questions that need to be satisfied is: *“Are there workable tools to ensure appropriate product utilisation?”* A pre-requisite for this is in the ability to obtain quality data within the limits of the approved indication and to minimise off-label use.

Centrally regulated tools that include, the Summary of Products Characteristics (SmPc) and Direct Healthcare Professional Communications (DHCP) provide guidance to prescribers. There are many other de-centralized tools, regulated at the member state (MS) level that can have a positive (or negative) influence on prescribing behaviour. These include registries, prescribing that is limited to certain hospitals, specialist certification of prescribers, diagnostic tools, etc. The availability, application and relative impact of these tools on prescription behaviour varies across MS and may present additional legal and ethical considerations for one or more stakeholders.

Work-stream D3.09 has explored some general ethical and legal issues that may arise through the introduction of the MAPPs concept, the implications for each stakeholder – in particular, patients and healthcare professionals (HCP) – and any liability change or shift between stakeholders and ethical considerations of prescribing control.

MAPPs is not an official designation and is not intended to create new regulatory or legal frameworks and thus presents no legal blocks per se. Physicians generally have the freedom to prescribe off-label where they feel it is in their patient's best interest; this is generally supported by legal frameworks within member states (MS) although reimbursement/payment may be restricted in off-label use. There remains a tension between permitting off-label use and managing a degree of control. On the one hand it allows earlier patient access where it may not already occur and incentivises the drive for R&D in other populations (i.e. paediatric). This is set against the need to retain a degree of control and structure in order to collect post-MA data to inform safety effectiveness and cost effectiveness measures to satisfy regulators, health technology assessment (HTA) bodies and payer requirements, and prevent unnecessary risk to patients. Any drive to restrict prescribing freedom under MAPPs must be balanced against the HCP's freedom (legally permissible or societal expectation) to act in the best interest of an individual patient. Additionally there is a question of whether patients who have responded well to treatment have rights to ongoing therapy should the benefit-risk balance change negatively for the population as a whole. This scenario may need to be addressed prior to starting treatment.

Creation of disease-specific registries offers the best option to collect the requisite long-term

data to support reduction in uncertainties for regulators, HTA, payers and patients, in order to be supportive of MAPPs. European Reference Networks provide an opportunity to create such registries for their diseases of interest, however there needs to be significant investment in infrastructure, the requisite expertise to collect RWD and information governance to permit cross border operations, which may not be practically or politically supported from every MS healthcare system. During data gathering, we heard concern from patients and HCP that the post authorisation requirements may widen the gap between those MS who are willing and able to engage in MAPPs compared to those who can't or won't.

Governing prescribing behaviour in public healthcare systems, where structured mechanisms exist and doctors are employees may be easier to implement, compared with private healthcare systems that may lack some of these structures. This raises ethical and legal concerns as to how enforceable prescribing tools may be in a completely private healthcare system outside of the centrally mandated tools, and whether a two-tier system may exist in countries with hybrid models.

Acknowledging that, as the evidence base evolves, indication expansion or contraction could occur, as part of the early multi-stakeholder dialogues and iterative development plan, there is an ethical and moral need for extra consideration for those populations that may have an alternative treatment option (however marginal) compared to those that have no alternative treatment option. How could or should the latter be dealt with remains a MS competency, with careful consideration of the population and societal expectations needed. It is acknowledged that this ethical scenario exists today with small populations and orphan products. However, there is an opportunity with MAPPs to utilize information set out in documents such as Managed Access Agreements that can detail such variables (e.g. patient eligibility, additional data collection needs and scenarios for continued access should reimbursement stop) which could both help guide the discussions and manage expectations between the patient and HCP.

As the concept of MAPPs evolves further, case studies of 'MAPPs-like' products in several MS would impart valuable experience of the prescribing tools used (or not used), how the ethical and legal challenges that arose were dealt with and how societal expectations can be accounted for in designing a prospective development plan for each product.

2. Introduction

Medicines 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.” (1)

The MAPPs concept is not an official designation and is not intended to create new regulatory or legal frameworks. It instead aims to make better use of various existing tools (such as conditional marketing authorisation (CMA)) and procedures for medicines development, reimbursement, on-market use, and post marketing-authorisation monitoring - through coordinated and repeated dialogue of the principal stakeholders.

ADAPTSMART is a multi-stakeholder consortium that was set up as a *Coordination and Support Action* under the EU Innovative Medicines Initiative 2. (1) In bringing together companies, universities, small and medium-sized enterprises, patient groups, payers and regulators in collaborative and pre-competitive projects, it aims to tackle Europe’s growing health challenges, and secure the future international competitiveness of Europe’s pharmaceutical industry. The ADAPTSMART consortium comprises all relevant stakeholders in the healthcare ecosystem: patients, academics, healthcare-providers, the research-based pharmaceutical industry, regulators, and health technology assessment (HTA) bodies. Some EU payers and payer organisations are willing to engage in constructive dialogue with the consortium.

2.1. Ethical and Legal Aspects of Prescribing and Use by Target Populations with MAPPs

MAPPs foresees an initial marketing authorisation (MA) - either as a CMA or a full MA in a well-defined but limited patient group. Under MAPPs, the lifespan approach to continuous knowledge generation throughout the on-market use aims to (i) achieve rapid reduction of remaining uncertainties around efficacy and safety, (ii) allow for broadening (or contracting) of the treatment-eligible population where justified, and (iii) inform payers about use and effectiveness in order to enable flexible pricing and reimbursement schemes.

As part of an early assessment by the medicine developer, and later dialogues with other stakeholders as to the justification of utilizing MAPPs for product development, a set of **Engagement criteria (Appendix 2)** have been developed (2).

As part of these engagement criteria, one question that need to be satisfied is:

“Are there workable tools to ensure appropriate product utilisation?”

One part of this relies on the ability to collect quality data from patients treated in the indication permitted – and to understand that prescribing practice is restricted to the indicated population specified – “on-label”.

Two key tools/systems exist for guiding appropriate use that are regulated at the centralized EU level. The Summary of Product Characteristics (SmPC) is the legal document that describes the intended use of a product in the agreed indication and target population. The Direct Healthcare Professional Communications (DHPCs), which can be initiated by MAHs or regulatory authorities and provide (new) important information on the use of medicinal products directly to individual healthcare professionals. There are many other tools/systems available that are regulated at the MS level that can have a positive (or negative) influence on prescribing behaviour such as registries, specialist certification of hospital or prescriber, diagnostic tools, etc. The availability, application and relative impact of these tools on prescription behaviour varies greatly across MS (3).

Additional factors that may influence prescribing at a MS level include the epidemiology of disease, accuracy of diagnosis, pricing and reimbursement structures, physician behaviour, point of dispensing (specialized hospital or doctor), legal responsibilities for long term follow up of patients, or societal expectations. Beyond the centralized tools to guide “on-label” prescribing it can be difficult to implement restrictions to limit “off-label” prescribing - HCP for the most part are legally unbound and free to prescribe “off label” (i.e. where a medicinal product is intentionally used for a medical purpose not in accordance with the terms of the marketing authorization - under their discretion and for the benefit of the individual patient (4)). Indeed, it may be desirable to develop knowledge for scientific and social benefit through therapeutic use other than ‘on-label’ – which might be the only treatment option for some patients with a high unmet need or no current treatment option.

Thus to satisfy the **engagement criteria** and guide prescribing or restrict it to targeted population(s) under MAPPs, this could open up additional legal and ethical considerations and uncertainties for some stakeholders, or magnify existing concerns that are above and beyond what already occurs today.

For example;

How can targeted prescribing be encouraged and enforced at a member state level? What are the legal and ethical implications if these control measures *are* or *are not* adhered to? Does liability shift between any of the stakeholders?

3. METHODOLOGY

The working group of D3.09 was led by consortium members CASMI and MSD. Consortium members that supported these deliverables included representatives from; Lysogene, EFPIA, Sanofi Genzyme, UCB, Bayer, Servier and the Merck Group. Initial internal discussions amongst this group led to a consensus of a number of potential ethical and legal themes that could affect one or more stakeholders that may arise under MAPPs. It was acknowledged that many of these scenarios do exist today, however concerns were expressed by some stakeholders that some may be magnified or have a greater impact to one or more stakeholders than today.

Briefly they are as follows:

Legal: i) the legal mandate to control prescription and prevent 'off-label' use, and how effective it is, and ii) the legal responsibility for long term follow-up and pharmacovigilance in patients.

Ethical: i) loss of patient access if confirmatory data is not forthcoming and how disengagement is managed, ii) differences in prescription control between public and private healthcare, and iii) maintaining the cycle of communication between HCP and patients.

These results were presented during a joint multi-stakeholder workshop on Jan 17th 2017 in parallel with deliverable D2.07 which surveyed the current 'prescribing tools' and their use and impact on prescription behaviour across MS (3). In the context of this work D3.09 explored the broader legal and ethical implications of prescribing in targeted populations, as well as the simple practicality in the various member states along with patients, HCP, ethicists, industry, regulators, HTA, payers, pharmacists and academics. Some additional guidance questions were provided to promote discussion (**appendix 1**). Thus the work of D3.09 should be understood in conjunction with work undertaken by D2.07.

The opinions expressed and the related discussions of D3.09 work are described below.

4. RESULTS

4.1 Legal Uncertainties

No legal barriers have been identified regarding products that would be approved through a MAPPs pathway. MAPPs is not an official designation - it is anticipated that the regulatory framework for granting a centralized marketing authorisation (whether a full MA or CMA) would not change. Therefore, any product will have met the regulatory standards of quality, safety and efficacy (i.e. positive benefit: risk demonstrated) as is the case today.

Regulation of off-label use

There is a tension that exists between the driving behaviors of HCP, patients and medicine developers as to the advantages and disadvantages of off-label use and the legal frameworks that may govern them. On the one hand off-label use can be permissive of better access to innovative treatments and the fulfilment of medical needs of patients, especially in cases where no other options are available. In order to steer the pharmaceutical industries to develop their products in an specific study population (e.g. children and adolescents), the European Commission has adopted a system of incentives: 1) "a six-month extension to the Supplementary Protection Certificate" and 2) "in respect of orphan medicines, (...) an extra two years of market exclusivity added to the existing ten years awarded under the EU's Orphan Regulation". (5)

From the physician's perspective, off-label use allows them to use existing drugs in an innovative way, when evidence exists, although a formal authorization did not take place. But by prescribing a drug off-label, the physician takes a special responsibility as they prescribe a medicinal product which has not been assessed by the competent authorities as being safe and effective in this specific use/population. The issue of liability in case of negative consequences of off-label use is a current concern for many stakeholders from different backgrounds and is a matter of national competency.

Physicians generally have the freedom to prescribe off-label and in a number of countries (e.g. France, Italy and Netherlands) off-label use is enshrined in national law. For example France operates a Temporary Recommendation for Use (RTU) for medicines that already have a MA in France in a different indication and are already commercialized in France (e.g. baclofen in alcohol dependence). A medicine developer can decide to withdraw its product because of the persistence of the off-label use (e.g. Pfizer and Cytotec). But sometimes, off-label use is authorized by the government for economic reasons. For example, in 2015, the French government decided to set up a RTU without the agreement of the developer (e.g. Avastin for ophthalmic indication)(5). While it is acknowledged that these challenges exist today, the ability to exert (legally binding) control of off-label use and the degree to which it is currently documented or can be accurately documented (either by physician, pharmacist or medicine developer) in any given MS will be challenging under MAPPs. Further empirical research is needed to understand not only the legal frameworks, but ethical frameworks and socioeconomic factors to prescription behavior across MS as all three are intrinsically interlinked. Understanding such factors beyond the practicalities of legal frameworks in, for example, in MS with lower GDP expenditure on healthcare would generate valuable knowledge gain with which to inform initial launch or indication expansion considerations as part of any given products prospective development plan.

Maintaining Access

There was concern expressed from some company lawyers and HCP that compared to today, an increase in the number of products with a CMA and/or with initially (very) small populations of high unmet need patients could be associated with a parallel proportional increase in legal challenges from patients seeking to force a medicine developer to provide access to a product beyond its (narrow) licensed indication obtained through an adaptive pathway. This could be either via initial access (e.g. off-label use outside of the initial indication) or maintaining continued access if later indication contraction or withdrawal occurs. While it is acknowledged that these scenarios do occur today - for example with orphan products (very small indications) - there remained a strong voice from patients as to the continuing legal responsibility of the HCP to put the best interests of an individual patient first, even if that conflicts with external pressures on their prescribing behaviour - to either further guide on-label use or prevent off-label use. Thus, throughout the product lifecycle mindset under MAPPs, the legal rights of patient 'responders' (to treatment) would need clarifying as part of the key initial and ongoing cycle of communication between patient and HCP.

Patient registries

All authorised medicines are subject to ongoing surveillance of safety using pharmacovigilance tools including via reporting of spontaneous adverse events and Periodic Safety Update Reports, and post-approval safety studies (PASS). However, in the case of medicines authorised with specific requirements for longer term documentation of efficacy and enhanced requirements for safety, particularly for small populations, as would be the case under MAPPs, the likelihood of the need to utilize cross border-border or international registries exists.

Individual marketing authorisation holders have, on occasion, established registries of patients prescribed their medicine, to collect long term patient data (product-specific registry). These have occasionally been 'all patients' where a known safety issue exists but are more commonly set up in selected hospitals and/or selected countries in order to achieve an appropriate sample size. These are often under the auspices of a professional society or a principal investigator. While this has the advantage of asking specific questions on a single therapy, it often lacks the flexibility to collect comprehensive data that is of sufficient value to answer HTA and payer questions such as the ability to compare incremental value of one drug vs other drug within a disease state. These are more likely to be served by a disease registry which can offer a more uniform way to follow patients longitudinally from diagnosis and study matters such as; the natural history of the disease, include patients from a matched but non-randomised comparator group, compare the sequencing of therapies and other treatment factors, and longer term safety and efficacy data. The exact nature of the data collection needed will be product specific and defined as part of the prospective development plan.

Creation of these disease- specific registries needs significant investment in infrastructure and the requisite expertise to collect RWD (e.g. Italy). Such support may not be forthcoming from medicine developers or be supported from the MS healthcare system - unless and until they have a clear need – and it requires additional information governance and access at a sophisticated and international level. For these reasons there was concern from patients and HCP of the political and legal implications that MAPPs may widen the gap between those MS who are willing to engage or can afford to engage in the requirements of products approved with conditions compared to those who can't or won't. For example, CEE countries with lower gross domestic product (GDP) expenditure on healthcare may not have the capacity or infrastructure to implement or run national disease registries thus would be at a distinct disadvantage to be involved in products developed under MAPPs. For rare diseases, the recently established European Reference Networks provide an opportunity to create such registries for their diseases of interest, whilst the more common diseases may be better served by academic units with an interest in epidemiology and access to a large population of well characterised patients in a well-connected healthcare system.

Whilst regulators require data on safety and efficacy, the data needs of HTA bodies and payers may include relative efficacy, the degree of healthcare resource use or the benefit of different sequencing of medicines. Registries need to be able to provide this additional type of data too, if decisions on continued reimbursement are to be made.

For products approved through an adaptive pathway, the use of disease registries as a tool to guide prescribing behaviour poses more unresolved practical considerations than direct ethical and legal issues of use as no one single model will suffice. The availability and use of disease registries is not specific to MAPPs when considering the conditions placed on companies for ongoing data collection. Regulators and companies will need to consider the practical options to meet the data needs of all stakeholders across the lifecycle of a product, cognisant of the feedback of patient groups on that, as desirable as long term data are, access to medicines should not be withheld where participation in a registry is not practical or desirable (see D3.08 for further discussion) (6).

4.2 Ethical uncertainties

Prescription control measures in public vs private healthcare systems

Healthcare provision and prescribing control is a national competence, with a variety of models ranging from a public provider (such as the UK's NHS) through to an almost completely private system with reimbursement through insurance or social security mechanisms (such as the Belgian sick funds (7)). Prescribing control – who is entitled and able to prescribe what - therefore varies both between MS and within MS. For example, many medicines only available with a doctor's prescription in the UK can be purchased at a pharmacy in Spain (without a prescription) provided the pharmacist is satisfied that the need is genuine.

Similarly, within country variation occurs depending on the healthcare setting. At a bare minimum, any qualified practitioner can prescribe any prescription-only medicine (whether in a public or private healthcare system). There are professional competency issues which are a matter of professional standards (and indirectly therefore, of ethical and legal concern) but nonetheless, a valid prescription from a qualified practitioner will be dispensed. Additional prescription controls are more likely to exist when working in a more governed environment such as a group practice or hospital, where the pharmacy department can implement an agreed policy or the institutional rules may restrict prescribing, for example only supplying an oncology medicine to the oncology department, or restricting prescribing of certain medicines to senior or otherwise accredited staff.

Marketing authorisations sometimes contain controls such as “medicine X should only be used by practitioners experienced in treating condition Y” but it is unclear whether these are enforced or enforceable in less controlled environments (i.e. individual or private practice). Under MAPPs this raises ethical and legal concerns as to how enforceable prescribing tools maybe in a completely private healthcare system outside of the centrally regulated tools of SmPC and DHCP and how that could translate to non-equitable patient access in public compared to private healthcare systems.

While this ethical scenario does occur today, when considering a strategy for products developed under an adaptive pathway, the ability to exert prescribing control measures are likely to work best, or be most easily enforceable, in managed environments such as hospitals and facilities with a clear governance structure. Conversely, where lone-practitioners are concerned, professional standards and peer review are likely to be the drivers which may indirectly but only retrospectively have legally enforceable implications.

Managing patient expectations

Patients and HCP consider that a clear understanding of benefit: risk balance and what happens if that balance changes are important ethical issues for early and continual dialogue between the patient and HCP. Similarly, loss of access posed a critical ethical challenge in circumstances where patients fell outside an amended indication, or reimbursement is withdrawn. As part of the early dialogues and iterative development plan there needs to be extra consideration for those populations that may have an alternative treatment option (however marginal) compared to those that have no alternative treatment options. How could or should the latter be dealt with remains a MS competency, with careful consideration of the population and societal expectations needed.

From the patient's perspective as well as other stakeholders such as HCP, MAH and HTA/P&R bodies, the information contained in a managed access agreement (MAA) could complement the informed discussions between HCP and patient as to the uncertainties relating to each product and how they will be managed. For example in the UK MAA exist for several specialist technologies (i.e. Duchenne Muscular Dystrophy). Contained in these legally binding agreements set out clear patient eligibility, data collection methods and monitoring, start and stop criteria to receive access, the intended length of access under the current agreement and what treatment path is available should treatment cease. Such mechanisms could be used on a product specific basis to help manage patient (and other stakeholder) expectations.

5. Recommendations and conclusions

For all of the above considerations discussed, there were no legal or ethical road blocks identified *per se* that were specific to MAPPs. Yet there remains a clear case for further empirical research of the legal tools available with which to enact prescription control, the ethical frameworks and related socioeconomic variables and expectations across a variety of MS. Outside of centralized tools to guide prescription, the use and impact of use (or non-use) of any given tool varies across MS and needs to be accounted for.

It is not possible to map all possible scenarios that may occur under MAPPs at this stage, thus further mapping of the practicalities of successfully guiding prescribing behaviour at a MS level could be gained through using detailed case studies of existing 'MAPPs-like' products. Understanding the legal tools and ethical frameworks available in CEE countries outside of those considered here and in D2.07 (i.e. middle to low GDP expenditure on healthcare) can

also better inform the practical implications of guiding targeted prescription with a product developed under MAPPs (MS with higher vs lower GDP). The most important gain would be how the above discussed ethical and legal issues were (or were not) dealt with within the context of an adaptive pathway.

The development of such a knowledge base is permissive in early stakeholder dialogues when mapping the lifecycle of a product and guiding targeted prescription – for example, from which MS to launch a product, through to indication expansion options. One enabler for this are the European reference networks as a knowledge platform to develop better designed disease registries that are fit for each stakeholder's evidentiary requirement needs. From this, more discrete solutions to the acceptance and transferability of MAPPs beyond a few selective MS can be devised.

APPENDIX 1

During Jan 2017 workshop, participants were presented with these additional questions to stimulate discussion of the broad ethical and legal issues

If it were desirable to restrict prescribing of a new medicine, through the MAPPs pathway, which of the following would be (legally) enforceable in your country?

- Limited to certain hospitals only, e.g. teaching hospitals
- Limited to certain doctors only, e.g. oncologists
- Prohibition of off-label use, i.e. illegal to prescribe off label
- Restriction of off label use i.e. considered outside professional guidelines
- Restriction off-label use, e.g. payer not reimbursing for off label use
- Provision of medicine ONLY if patient agrees to safety data collection (e.g. in registry)

APPENDIX 2

Engagement criteria from D2.03

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

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

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