



Ethical and Legal Aspects of Adaptive Decision Making

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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
CMA	Conditional Marketing Authorisation
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
EuNetHTA	European Network of HTAs
IP	Intellectual Property
P&R	Pricing and Reimbursement
GMC	General medical council
GMP	Good medical practice
GMPPD	Good medical practice professional development
EPAR	European Public assessment report
EUPATI	The European Patients' Academy

1. Executive Summary

Medicines Adaptive Pathways to Patients (MAPPs) can be viewed as an engagement framework with which stakeholders collectively - through coordinated and repeated dialogue - prospectively plan and use various existing tools and procedures for medicines development, marketing authorization (MA), reimbursement, on-market use, and post marketing monitoring, in a lifecycle approach¹. Thus MAPPs seeks to foster access to beneficial treatments addressing an unmet medical need at the earliest appropriate time in the product life-span in a sustainable fashion.

MAPPs is not a new designation, but will operate within the existing legal and regulatory framework, making better use of existing tools, processes and authorisation routes. MAPPs products will have a MA with a minimal data package that allows authorisation, in small populations and with the need for long term data collection, similar to the situation today, for example, with conditional marketing authorization (CMA) or orphan products.

Within the ADAPTSMART consortium, the remit of work-stream D3.08 has been to explore 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 what recommendations could be made to mitigate against identified issues. Specific legal issues relating to intellectual property law are the subject of another ADAPTSMART work-stream and are not discussed here.

This work stream did not identify any general legal blocks to the MAPPs process, fundamentally because such products are deemed to have reached the required regulatory standard for market authorisation (MA) (albeit within a small clinical indication). Thus it is considered that there is greater chance that the benefit: risk assessment at MA approval will change with time, as more information on the product accumulates. Concerns from medicine developers and HCP were raised that liability claims or legal challenge from patients may increase as a result, although it was acknowledged that liability claims could occur under these scenarios currently.

We found little evidence that prescribers knew the legal status of medicines they were prescribing – whether conditional or full (standard) MA. An educational opportunity exists to inform prescribers, so that they in turn can explain to patients the novel nature of a MAPPs product, the degree of (un)certainty, and how it will be managed. Prescribers also need to maintain an up-to-date knowledge to avoid the accusation by a patient that they have not been informed of a potential risk or change in risk which had, nonetheless, been identified to prescribers in approved regulatory materials.

Likewise no new ethical issues have been identified per se that are specific to MAPPs, but a number of existing ethical challenges that are present today - with small or restrictive populations based on disease or geography, and an emerging post-authorisation evidence base (e.g. CMAs, orphan products, etc) - were considered potentially more likely to occur, or have a greater impact to one or more stakeholders. Examples include: the need for ongoing data collection and the patient and HCP burden this entails, the degree and format of information available to patients in order to make an informed decision, implicit or explicit

patient consent to treatment, the societal need for ongoing data collection to reduce uncertainty set against the patients right to opt out of data collection without jeopardizing access, and issues around enacting and maintaining equity of access across healthcare systems in different Member States (MS).

None of these legal or ethical uncertainties are considered to be a block per se on progress towards a better use of adaptive design and adaptive licensing. However, these uncertainties require more careful and prospective consideration, taking into account the divergences that may occur on matters which are national MS competencies rather than those that are governed at centralised EU level, and the ethical and legal frameworks that govern those differences - for which further research is needed.

2. Introduction

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.

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)

MAPPs is not a new designation. It does not create new regulatory or legal frameworks. Instead, MAPPs describes the prospective and planned use of various existing tools and procedures for medicines development, marketing authorization (e.g. CMA), reimbursement, on-market use, and post marketing monitoring - through coordinated and repeated dialogue of the principal stakeholders.

Thus, "[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."(2)

It should be remembered that the authorisation of new medicines is generally undertaken at an EU level using the centralised procedure, or by mutual recognition using the decentralised

procedure. National licensing is unusual for new medicines. However, matters relating to prescribing rights and restrictions, delivery of healthcare, and (importantly) EU member state reimbursement remain a national competence.

2.1. Ethical and legal uncertainties overlap and affect different stakeholders differently

New concepts such as those proposed under MAPPs – i.e. the use of multi-stakeholder dialogues, prospective, iterative development processes, and early appropriate access to a medicine - brings potential challenges and raises uncertainties in both legal and ethical aspects, which may affect one or more stakeholders. Work-stream D3.08 has been exploring these general issues through semi-structured interviews and consensus building with stakeholders such as healthcare professionals, industry, regulators, HTA bodies and patients (including patient organisations).

Legal uncertainties have been considered from a number of stakeholders' perspectives – the pharmaceutical company, the regulator, the prescriber, the healthcare institution, and the patient - generally asking the question, “If something went wrong, where would liability rest?” and then asking, “How might this differ from today, under MAPPs?” The prime consideration has been around safety and efficacy (and any subsequent changes to this) but we have also considered matters such as access to the medicine after MA, and requirements of patient level data collection and participation in registries. Whilst acknowledging its existence in this context, we have not considered legal matters such as intellectual property and regulatory data protection, which may be impacted by earlier MA and patient access.

Ethical uncertainties have generally paralleled the legal discussions, but looking less at, “Is it legal?” and more at, “Is it right or fair?” Issues considered have included consent to treatment, whether treatment is considered to be closer to standard of care or to a clinical trial, equity issues - should a product be available in one region or MS but not another - and what issues arise if a product withdrawal occurs, or if the benefit: risk balance changes.

2.2 Background

There is a broad spectrum of published work on the ethical perspectives of early patient access to medicines that cover issues including: addressing uncertainty, benefit: risk balance, personal data protection and considerations of patient involvement in medical research (3-7). Likewise, there is some literature covering: legal frameworks of personal data collection and its use, informed consent to both treatment and clinical trials, and off-label use and liabilities (8-11). However, to date, there is a lack of literature relating to ethical and legal implications in the context of adaptive pathways or MAPPs. This reflects the reality that MAPPs is still a relatively new concept which is rapidly evolving. An understanding of the range of perspectives regarding the ethical and legal issues is yet to be fully achieved.

In 2016, CASMI produced a report on patients' ethical perspectives of MAPPs across 3 disease states (oncology, neurodegenerative and rare disease)(12). From in-depth interviews and

workshops, a number of issues became apparent that warranted further study. These included i) equal availability of a medicine to all patients once evidence of safety and efficacy was available ii) the implications for consent and the potential blurring of the boundary between clinical trials (where uncertainty is higher) and clinical practice (where uncertainty is lower), and iii) protection of patient data and its use within the legal framework of data privacy laws.

The output of this original work formed the basis to build upon under this program of work and explore ethical and legal challenges relating to MAPPs, and how those challenges may affect each stakeholder differently. To this end, the remit of working group D3.08 focused on “ethical and legal aspects of adaptive decision making and recommendations on how these can be addressed”. The D3.08 work stream initially explored these issues via a number of in-depth informal interviews from various stakeholders. On January 17th 2017, these results were presented and a consensus was reached during a multi-stakeholder workshop in London, UK - the output of which forms the basis of this paper.

The results and recommendations presented here are intended to illustrate key multi-stakeholder concerns of general ethical and legal uncertainties relating to MAPPs, and highlight a number of concerns that, although may be present today, are considered likely to occur more frequently or have greater impact on one or more stakeholders, under adaptive pathways. It was not our remit to perform an in-depth analysis of the existing ethical and legal frameworks within each MS. Such work may form part of the basis for future research questions relating to transferability of concepts and recommendations.

3. Methodology

3.1 Approach

The working group of D3.08 was led by consortium members CASMI and MSD. Consortium members that supported these deliverables included a total of nine people from Lysogene, EFPIA, Sanofi, UCB, Bayer, Servier, and the Merck Group. EMA provided feedback on initial internal discussions, however was not involved in the below described interviews and is not an author of this document. 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. Briefly they are as follows:

Legal: i) Patient data privacy, access and use, ii) informed consent, iii) changes in both liability and burden to the prescriber, medicine developer, regulator, pharmacist, and health insurers, iv) promotion and marketing of the product (by either the HCP, medicine developer or patient organisations), v) intellectual property and regulatory data protection.

[Although legal concerns of Intellectual Property and Regulatory Data Exclusivity were identified here, these topics were outside the remit of D3.08 and have been explored in detail under another working group, D3.06]

Ethical: i) Informed consent, ii) patient data privacy, access and use, iii) patient engagement and cycles of communication, iv) patient and public perceptions of industry, health providers, and government, v) patient burden for ongoing data collection, vi) patient eligibility, vii) uncertainty of safety, or safety not as expected, viii) clinical and treatment equity, ix) public vs private funding for drug use by patients and, x) promotion and marketing of products by medicine developer, HCP, or patient organisations.

Since there was initially a large number of diverse issues and themes identified, we conducted semi-structured interviews with a much wider audience, in order to identify which issues or themes were the most commonly reported as being of greatest importance or greatest impact, and which stakeholder group would be affected. The refined group of themes were explored and validated at a large multi-stakeholder workshop.

3.2 Semi-structured interviews and Analysis

Group members conducted semi-structured informal interviews either one-to-one or as a group of 2-3 (max) from a pool of colleagues, partners and collaborators. The questions were checked by an independent researcher for bias and language*(see appendices). The interview slide deck was sent to the interviewee 2-3 days prior to interview. At the start of the interview, the concept of the MAPPs pathway and how it may differ from the current pathway was explained.

The interviewer used the slides and supporting documents to further prompt the interviewee for their opinions on specific ethical or legal topics. Responses were anonymised and responders were only identified by stakeholder group. A total of six questions were asked for the ethical implications and again separately for legal implications, and are listed in **Appendix 1**.

Expert opinions were transcribed from written notes, and analysed (by an independent researcher*) using a thematic analysis framework method, which identified the themes for each factor at their respective structural organisation levels (13). Several major, distinctive themes (i.e. those that were reported most frequently) emerged from ethical and legal sectors with some common and overlapping issues. Another set of distinctive but minor themes (i.e. reported less frequently) also emerged from experts across ethical and legal sectors, with more distinct divergence between themes.

Results were presented (**Appendix 2**) during a joint multi-stakeholder workshop on Jan 17th 2017 with patients, HCP, ethicists, industry, regulators, HTA, payers, pharmacists and academics. Three hypothetical case studies were used (**Appendix 3**) to assist in consensus building around the key themes. A set of recommendations to manage these issues were developed during the workshop.

4.1 Overall results and recommendations

4.1.1 Legal Challenges

No general legal barriers have been identified regarding products that would be granted a marketing authorisation (conditional or full) where the development has followed an adaptive design. Since “MAPPs” simply describes an iterative and interactive route to a marketing authorisation, rather than being an authorisation category per se, products will have met the regulatory standards of quality, safety and efficacy (i.e. positive benefit: risk demonstrated) as is the case today, and thus legal risk per se should not change

Nonetheless, in terms of legal uncertainty, by virtue of the narrow population, the small absolute numbers studied or the duration of follow-up, it was considered that there may be an increased likelihood of a change in post MA benefit: risk, or efficacy and safety assessments which could result in additional cautions, warnings, restriction or loss of access, or product withdrawal for economic reasons. It is noted that this could be the same with other products approved on small numbers or short duration of follow-up, regardless of whether the route to authorisation was adaptive.

We heard concern from some company and general medical lawyers that this could be reflected in an increase in the likelihood of litigation (e.g. from a patient to a pharmaceutical company, or regulator). Liability for defective products (Directive 85/374/EEC) maintains its status quo with the manufacturer or MAH most likely to be at risk of being sued by patients - the generally accepted principles of standard legal defence would apply, as is the situation today.

As the channel between information provided by the pharmaceutical company and approved by the regulators (e.g. Summary of Medicinal Product Characteristics, package insert), the HCP plays a crucial role in conveying and explaining the relevant information relating to the product and treatment regime, so that consent to treatment is based on a patients' understanding of the known benefits, risks and uncertainties. But consent (implicit or explicit) also allows the physician to demonstrate that he/she has done his/her duty to provide the most correct and up-to-date information. We found little evidence that prescribers knew the legal status of the medicines they were using – whether conditional or full marketing authorisations. There is clearly an educational opportunity to inform prescribers, so that they in turn can explain to patients the novel nature of the product, and the degree of certainty or otherwise that exists. With a rapidly evolving evidence base for a given product, it is important that prescribers maintain an up-to-date knowledge to avoid the accusation by a patient that they have not been informed of a potential risk or change in risk which had, nonetheless, been identified to prescribers in approved regulatory materials. For example products which have a conditional MA, also would have a 'black triangle' symbol on the SmPC – indicating that this product is under specific extra surveillance due to the nature of the data available at the time of authorization.

4.1.2 Ethical challenges

Consent to treatment

Products approved through an adaptive pathway will have an MA (likely either a Conditional MA or full MA in an initially restricted population), with a reduction in uncertainty and confirmation of a positive benefit: risk as post MA data evolves. Provision of adequate information to enable a patient to make an informed decision is seen by patient groups as a critical element to successful implementation and mitigation of both legal and ethical uncertainties within the context of MAPPs.

During the various workshops and input sessions, particularly with patient representatives, there was a call for adequate information to be provided on the benefits and risks of a new medicine before a patient agrees to treatment. Whether this agreement should take the form similar to routine care - verbal, implied/informal - or something more akin to that of a clinical trial - written, explicit/formal - is inconclusive, and indeed it may vary from product to product. There is a need to clearly communicate to the patient the distinction between consent for participation of a clinical trial (where uncertainty of efficacy and safety exists) versus that of consent to treatment to a novel therapy which, whilst authorised, is nonetheless new and for which the full efficacy and safety dataset are still maturing.

We heard repeatedly from patient representatives that provision of information and documentation of consent - beyond that of just implied consent - should take place. These should include: the currently known and anticipated benefits, the currently known risks, the uncertainties (e.g. a lack of large scale or long term data at the time of access), the possibility of product withdrawal, or restricted availability in the event of a negative change in the benefit: risk balance, or for commercial reasons. While all of the above issues could arise today with products that have a CMA (or otherwise), in practice, despite the 'black triangle' symbol for denoting a product undergoing enhanced surveillance, prescribers are rarely aware of the MA status of a particular medicine (for example if it has a conditional MA). Thus it is considered even more important than today that the regulatory status of a product is known to a prescriber, including the nature of ongoing data collection. Therefore, this area requires better and more structured education for prescribers regarding the emerging evidence base on a product-by-product basis. This could be facilitated through better use of relevant prescription materials and educational documentation such as treatment guidelines and Direct Healthcare Professional Communications (DHPCs). This could in itself be enabled by the respective competent authorities and HCP umbrella organisations in the MS.

Additionally, it is acknowledged that while it is common practice for surgeons to provide patients with the pros and cons of a surgical procedure (in line with some of the above mentioned reasons), followed by documenting the informed consent process, by nature of their role, this same practice is less common for physicians (where consent is often informal or implied). The consent process between patient and HCP is a very complex process due to the variances in its contextual application. Therefore, training and tools may be needed to facilitate a more detailed consent process for products undergoing an adaptive pathway to mitigate some of these concerns.

Use of registries as post authorisation tools

Given the likelihood of a need for ongoing post-MA and post-access data collection to confirm efficacy and safety, and for (relative) effectiveness and cost effectiveness, the use of patient registries is an aspiration as an enabling tool for data collection on products approved using a MAPPs approach (acknowledging MS differences in HTA/payer remit and structure). The proportionate use of post-authorisation safety and efficacy assessments, which may include registries, is generally accepted. Whilst it is highly desirable for products that have used an adaptive pathway to approval to be the subject of careful surveillance and for confirmatory data to be collected and analysed, there is ethical tension between an individual patient's right to consent to their data being collected and used (or not), and that of the broader societal need to collect more data (for example, safety and efficacy for regulators and medicine developers, and (relative) effectiveness and cost effectiveness for payers) to support the reduction of uncertainty. From a legal perspective patients voluntarily enter a register and consent for processing of their data in registries cannot be mandated as a precondition of access to a medicine. Thus, there remains concern from patients surrounding which circumstances, and to what extent extra patient data would be collected for MAPPs products. For example, the distinction is needed between data collected under conditions of an individual's standard of care, (e.g. CT scan every 6 months to assess progression) versus interventions that benefitted society's need to demonstrate broader safety, efficacy and cost effectiveness measures. If data were to be collected on a product-specific basis for the latter, then it could form the basis for example, a clinical trial or Post Authorisation Safety Study, which presents an extra patient burden, obligation and expectation that would require prospective and continued transparency and clarity. This dilemma can be partly mitigated by improved patient education as to the importance of data collection for example, through direct HCP interactions or via umbrella patient organisations and patient driven educational initiatives such as, The European Patients' Academy (EUPATI). In addition, exploring flexible approaches to longitudinal data collection, such as disease registries, data extraction from electronic health records, or the provision of data by the patient through an App, for example, could be permissive.

Patient level data subject right, and whether pharmaceutical companies have access to it, is considered to be of a lesser concern per se. The development and use of longitudinal disease-based registries where treatment in a specified field is preferable to that of product-based registries. Making use of existing European networks and registries (and cross-border data sharing initiatives) to support MAPPs should be explored in this context, rather than creating bespoke registries per product.

Thus there remains a tension between a patient's desire for a *consent to treatment* being more than something that is simply implied - but not to the formal level of a clinical trial (due to the registered status of a MAPPs product) - together with society's need for a patient's entry into a registry to facilitate additional data collection (that is akin to, for example, a Post Authorisation Safety Study or clinical trial) which requires a formal *consent for data collection and use*, with the right to opt out of that consent without jeopardizing access. The preference

from patients is for an opt-in decision-point – “do you agree to your data being collected” rather than a default of - “you do agree to your data being collected”.

A similar tension exists in other early access schemes like the UK’s EAMS – and is being addressed through creation of decision trees for medicine developers and educational material as to what type of patient data is needed and when it is collected. Learnings from this and similar initiatives could be shared here.

Equity of Access to Medicines

Irrespective of the route to authorization, variation in the availability of a medicine from country-to-country is seen as a substantial ethical problem. Access to a specific medicine, funded by the MS health system, is a national competence and may be a decision at the national level (e.g. Germany) or sub-national level (e.g. England and Scotland), or local and hospital level (e.g. Spain). Likewise, whilst current cross-border legislation (EU Directive 2011/24/EU on the application of patients’ rights in cross-border healthcare) allows patients to travel for treatment, it does not facilitate access to treatments that are not available in one’s home country. For example, a gene or cellular therapy (as such likely to benefit from an adaptive pathway approach) may only be available in a single specialist center in one MS only. Member State-specific access to promising treatments, whilst not a new issue, requires careful consideration under MAPPs; in particular, between countries who have higher vs lower GDP expenditure on healthcare (for example some CEE countries). The underlying factors dictating differential access to new (transformative) medicines are multi-factorial and include; P&R considerations (price, affordability and how healthcare ‘value’ is defined in each MS), different HTA and payer processes, degree of investment in healthcare, ethical frameworks, availability and use of data collection infrastructures (inc. registries), the extent of (any) cross-border collaborations, availability and impact of prescription tools and methods, and societal preferences. For particularly rare conditions, the clinical expertise may also not reside in all MS, and thus cross-border opportunities (such as joint platforms) become more important, and if lacking may become more prohibitive for access.

The most powerful driver of these factors will be P&R considerations. It is predicated that highly transformative products, such as those likely to reach a conditional marketing approval by an adaptive process will have a minimum data set but may have a high price, may be applicable (at least in the first instance) in relatively small populations, and require continued data collection to confirm benefit: risk. This is true too, for many orphan products today. It might be expected that MAPPs products may be more likely initially to be fully reimbursed in MS where expenditure on healthcare is relatively high, where data infrastructures are better established and permissive for long term post MA data collection, and HTA/payer authorities’ processes allow flexibility and resources to be involved in the early and continued multi-stakeholder dialogues of an adaptive approach. Thus some MS with relatively lower expenditure on healthcare could be at a distinct disadvantage and unable to facilitate equitable access to these new medicines.

Optimizing cross-border initiatives such as cross-border data sharing, utilizing disease registries, and joint platforms such as EUnetHTA - which already includes some CEE countries would strengthen the understanding of some of the barriers, and facilitate strategies to improve the transferability of such products more broadly across MS.

Early dialogue with all stakeholders is seen as critical in addressing the above issues where possible. Dialogue with HTA bodies and national payers is seen as important to understand how cost effectiveness could be assessed for such products, where uncertainty of long term benefits and risks is seen as a challenge to reimbursement decisions - flexible pricing models are seen as one way forward. Likewise, early dialogue with patient organizations is also critical for all stakeholders to understand the impact of the new medicine. Patient organizations in particular, urged flexibility on the part of industry, HTA bodies and payers, to ensure equitable access across disease status and across MS.

There is an acknowledgment that there would be occasions where a product was no longer commercially viable, or did not demonstrate clinical outcomes that supported its cost-effectiveness, so that continued access would cease. There is a risk that such decisions are not uniform across the EU, further increasing inequitable access. There is also likely to be a difference in how patients already receiving a medicine are treated, compared with patients yet to be started on a medicine, despite identical clinical profiles. To address and prepare for such situations, a strategy should ideally be prepared at launch to address all stakeholders' concerns, particularly those of patients and HCP, regarding continuity of treatment. For example, in the UK, in some instances where patient access is granted but later demonstration of cost-effectiveness is lacking, access remains for those patients already on the medicine, but no new patients have access. In cases of withdrawal due to changes in effectiveness (and hence cost effectiveness), a multi-stakeholder agreement could be envisaged to explore continued access for those patients already being treated. The nature of such an agreement would require further exploration.

Information and Patient Education

Access to reliable information is considered key to mitigate against patient uncertainties on ethical and legal matters. Information and communication about adaptive pathways and the nuances of MAPPs, among patients and civil society, represents a common underlying basis for the above-mentioned themes - it requires a continued dialogue with other stakeholders to ensure ongoing and accurate mechanisms to disseminate information effectively. Informed and educated patients would be more empowered and able to participate as equal partners in shared decision-making regarding the choice of therapy; and it would increase their willingness and ability to contribute to the ongoing data collection.

5. Recommendations and conclusions

Education of all stakeholders about (MAPPs) product status

There is a real need for prescribers and physicians in particular to be educated about matters such as conditional MA, how that differs from a full MA, as well as the routes to those approvals (e.g. positive benefit: risk with a comprehensive data set compared to a less comprehensive data set). This would help them understand why a product is restricted to a small indication initially and how that may affect the possibility of product restriction (including, in the extreme, withdrawal), and the desirability of ongoing data collection, etc. Provision of patient level information (including the above) prior to consent to treatment needs to be done in a language-specific, health literate way. Patient organisations can help and should be involved in co-creating such materials and through training and education programs such as IMI's EUPATI initiative. Educational material for prescribers (e.g. outline of approval status, the level and type of ongoing data collection needed, and points to include in discussing treatment options with patients) could be developed by the manufacturer and form part of the regulatory package. This could be complemented by, for example, proactive dissemination of information available on the medicine developers' website and company dossiers that is in line with MS processes. Educational material for patients (e.g. outlining the risks, benefits, data requirements, etc.) could be developed by the MA applicant in partnership with patients in a health literate manner, and made available to all users. Consideration for both of the above should also be given to new modalities of patient centric communication such as apps, and videos - not simply written information. This is an important part of the evolving landscape of patient involvement and may account for hard to reach patient populations (i.e. rare diseases, young or elderly). Partnering with new platforms such as IMI's initiative on enhancing patient engagement across the lifecycle of medicine development (PARADIGM) will be key.

Managing data collection

Each product approved through an adaptive pathway should prospectively outline its data collection strategy to document post MA safety and efficacy. There is justification to consider restricting access (at least initially) to centres of excellence where disease-specific clinical expertise and data collection infrastructure is generally optimal and permissive for confirming the benefit: risk profile and for example, demonstrating cost effectiveness in the initial indication. However, from a patient-centric point of view, expertise and data should travel, and not the patient. Participation in registries, etc. should not be mandated or made a condition of access, thus a mechanism for initial or continued access outside of these registries is needed. Patient driven (i.e. via EUPATI) and HCP driven (i.e. via DHCP) material can educate as to the rationale for data collection generally and that which is product specific. Data collection therefore, should be streamlined, flexible, internet-based (where possible), and interactive with other data sources such as carefully designed disease specific registries and data extraction from electronic health records. A survey of HCPs (Work package 3) suggests that they seem ready to generate post approval data collection for products developed under MAPPs. As part of the data strategy and controlled distribution, MA holders should consider using centres of excellence, including the European references network

(ERN) sites. Data collection that requires non-clinically-indicated investigations are likely to represent interventional clinical trials, unless the additional patient and HCP inconvenience/risk is minimal (or facilitatory structures and processes are in place). Further strategies for optimizing real world data (RWD) collection and streamlining cross-border initiatives are detailed in other IMI initiatives – BD4BO and GETREAL, for which future research efforts here should align closely with.

Maintaining equity of access

The ability to maintain equitable access can be partly augmented through early and continued dialogues with patient organizations, in order for all stakeholders to understand the impact of the new medicine and any subsequent changes to that access. Clearly, if the benefit: risk balance should become less favourable in time, regulators retain the right to further restrictions on availability, and companies retain the right to change decisions of availability based on economic assessments. The impact of these decisions on both existing patients and on potential recipients will need to be addressed on the basis of the new data, and should be uniform across member states. Early dialogues with all stakeholders will help clarify the product specific issues and embed mitigation strategies to address this. Additionally utilizing expertise and critical mass from platforms such as EUnetHTA (that include some CEE countries) would facilitate broader strategies to improve the transferability (and accessibility) of highly transformative products (inc. those under MAPPs) across MS.

For all of the above recommendations discussed, there remains a clear case for further detailed research of case studies of existing ‘MAPPs-like’ products that are available across selected MS, that have either high or low GDP expenditure on healthcare, in order to assess the practices and ethical and legal frameworks that are currently in place and how the above issues were (or were not) dealt with. From this, more discrete solutions to the acceptance and transferability of MAPPs can be devised.

Appendix 1

Interviewees were broken down into the following groups: Legal- Company lawyers (3) Regulatory affairs (1), Medical lawyers/litigation (2), Patient reps/advocates (2), Ethical-regulatory affairs (1) HCP (2) Company or academic ethics/bioethics (2), patient reps/advocate (1).

Below are listed the semi-structured interview questions used to identify ethical and legal concerns.

- 1) Please summarise your area of work.
- 2) Do you have examples of where you/ your organisations have been involved in drug development and patient access where the current system / framework caused ethical concerns?
- 3) Do you have examples of where you/ your organisations have been involved in recent explorations of the ethical concepts of adaptive pathways or early access to medicines?
- 4) If a drug received an initial Marketing Authorisation via a MAPPs pathway what ethical implications do you foresee and for which stakeholder groups do the issues apply?
- 5) Do the ethical dilemmas posed by MAPPs differ from those associated with current drug development processes?
- 6) Are there types of therapy or circumstances in which MAPPs would not be appropriate on ethical grounds?

Appendix 2

Tables of interviewee responses to legal and ethical concerns

The following tables represent the major and minor legal and ethical themes identified from 14 interviews (8 legal and 6 ethical – see appendix 1). **The themes presented here consist of issues that were raised by the interviewees that were either specific to MAPPs, or more commonly, issues that exist today but were considered to be of greater likelihood of occurring/have greater impact than would be the case today**

*Suzanne li, CASMI undertook the independent verification and analysis.

Major = most frequently reported theme

Minor = less frequently reported theme

Table 1: Major Legal Themes

Legal Concern	Stakeholder it impacts	Reason
Increased likelihood of liability action against prescribers (HCP)	HCP, Insurers Patients	If post MA data does not confirm the positive benefit: risk of initial MA, or if harm is done, clinicians may be held responsible. Would current indemnity cover this?
Changing liability responsibilities of each stakeholder during lifecycle of product	HCP, Manufacturer	Sponsors are responsible for drugs in clinical trials, but the inherent uncertainty is stated and consented to by the participant. No-fault indemnity may be in place. This is generally less so, post MA, if used in accordance with label.
Formal approach to informed consent	HCP, Patients	Clinicians need to formally review and discuss information with patients to protect themselves. Patients need to be made aware of all the risks and confirm (sign/initial) that they understand them*.
Increased likelihood of patient litigation : ineffective treatment, negligence, inaccessibility to drug	Patients, HCP, Insurers	Patients may file a negligence claim, may sue or file a consumer protection claim for ineffective treatment, negligence or inaccessibility to drug
Restrictions or guidelines for appropriate prescribing	HCP	There are current guidelines that prescribers can and should follow regarding levels of specialist expertise required, facilities available when prescribing certain medicines (e.g. GMC, GMP, GMPPD). Few are binding and fewer still are fail-safe.

*The degree to which patient consent to treatment is informed, obtained and documented varies in routine health care (compared with the formal written informed consent of a clinical trial). How does this apply to a MAPPs approved product where uncertainty may still exist?
The form of consent to treatment (implied or formal) was debated by the interviewees and the working group (see discussion).

Table 2: Minor Legal Themes

Legal Concern	Stakeholder it impacts	Reason
Additional financial burden of liability insurance	Manufacturer	Pharmaceutical companies may need more expensive liability insurance than the clinical trial insurance that is used.
Patient data privacy, access and use	Patients	Patients may be concerned with the data being collected, how it is collected, stored and used. Can participation in a data collection activity (e.g. registry) be mandated in order to access a particular medicine?
Appropriate pharmacovigilance system	All Stakeholders	Are current post marketing pharmacovigilance activities appropriate for a MAPPs-approved medicine where more active surveillance may be more appropriate?

Table 3: Major Ethical Themes

Ethical Challenge	Stakeholder it impacts	Reason
Informed consent: -Formal process for transparency -Mandatory for data collection and access - RCT vs standard of care	Patients, HCP	Patients need to be made aware of the implications associated with the uncertainty at time of consent e.g. unknown side effects and/or no efficacy, potential of withdrawal of the treatment and the possibility of data collection being a condition of drug access What type of consent is needed – the same as RCT consent or that of standard of care
Patient communication: -Clarity of information available to patients	Patients, HCP	Comprehensive, clear information for patients about the drug development, treatment options and access. Identified that HCPs (and subsequently patients) are not well versed in conditional authorizations etc. Current communication platforms do not allow for up-to-date communication to be shared with patients in real-time
[Ethically] Acceptable level(s) of risk with early patient access	All Stakeholders	Risk and uncertainties need to be documented and based on ethical principles or the ethical review guidance Reinforcement of scientific rigour is needed
Long term patient surveillance and reassessment: -Continued patient	Patients	Practical concerns exist about long-term follow-up and/or an exit strategy. These issues need to be specified and a framework put into place. Viability and validity of registries –who/what

surveillance of benefit: risk -Surveillance upon patient 'exit' (choice or imposed)		maintains?
Transparency of Benefit: Risk	All Stakeholders	Concise information needs to be put in place about recruitment and the benefit: risk of the program or product. Need to have a transparent framework in place**.

** For authorised medicinal products a European Public assessment report (EPAR) is published reflecting outcome of scientific assessment

Table 4: Minor Ethical Themes

Ethical Challenges	Stakeholder it impacts	Reason
Equity of treatment	Patients	Initial MA (in restricted population) would have to consider on a case-by-case, medicine-by-medicine basis. There could be staggering to include different patients with varying levels of disease severity and age to give all an opportunity to have access.
Equity of benefit (individual vs collective benefit)	Patients	If there is a negative clinical trial outcome for a drug (it cannot be excluded that it can benefit other patients), the drug could potentially benefit other patients -‘True affect’ in the minority of people and a ‘truly negative affect’ in the majority of people.
Equity of access	Patients	Patients falling outside of the eligibility criteria are vulnerable to major ethical considerations, particularly when there is no other alternative and the other option is an early death
Inconsistent perspectives of ethics committees	Researchers/ Academics	Different ethics committees within and across MS have differing perspectives regarding ethical concerns, hence there is a risk of receiving <i>clashes</i> of opinions between different ethics committees regarding the same ethical question.
Transparency of process (health system vs industry)	All Stakeholders	The costing of the medicine should reflect the multifaceted nature of costs - medicine developer costs and any public health system contribution to its development and access. With public health systems, costs should be a transparent and a fair process.
Treatment - standard of care vs RCT	HCP, researchers	What counts as standard of care practice and RCT (research)? The lines may be blurred because the duties are different between doctors and researchers
Appropriate pharmacovigilance system (under	Patients	Patients may be more vulnerable in MS where pharmacovigilance reporting is less common – may need to be enhanced pharmacovigilance

greater uncertainty)		reporting. Need to report all adverse events.* Off label and compassionate use – how is this accounted for with pharmacovigilance reporting? Could this be utilized as a learning opportunity
Severe disease conditions Applicability to non-pharmaceutical treatments?	Patients	Needs to be a MAPPs structure for the most debilitating diseases that require new types of therapy: gene, cell, etc.
Ethics and its definition	Regulators	There are different uses of ethics and application to various issues.
Time points (moments) of Ethical evaluation	Patients, HCP and regulators	Moral/ethical evaluation time points are required to complement scientific evaluation time points- e.g. Evaluating the ethical needs of patients for alternative treatments).
Learning health systems	Patient groups, HCP	Patients are enthusiastic at engaging in learning healthcare systems. They should however still have best care/practice available to them even if they do not engage in learning health systems (e.g. taking part in research)
Unpredictable results	Regulators, HCP, patients	Need to have a robust data capture system in place that can be changed as ethical issues change over time
Appropriateness of disease	Patients	MAPPs is appropriate for life threatening diseases (and those classified as high unmet need**) and confirming the benefit: risk of the product
Understanding increased uncertainty	Patients, HCP	How would the increased uncertainty [related to an emerging evidence base] be explained during consent between patients and clinicians?
Technology restriction	Patients, HCP, regulators	MAPPs concepts would be difficult to apply to innovative technologies

* 2010 PV amendments to Directive 2001/83 addressed this issue via the inverted black diamond on all medicinal products for at least the first five years after marketing approval - and included AE reporting information in the package leaflet for patients.

** " 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.**" – Definition from ADAPTSMART Glossary of terms and also from Regulation 507/2006 on the CMA: http://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2006_507/reg_2006_507_en.pdf (see article 4.2)

Appendix 3

Below are listed 3 hypothetical case studies that were used to Jan 17th workshop to stimulate discussion of the ethical and legal issues at hand. An additional set of scenarios was later used to stimulate discussion on possible recommendations

Hypothetical case study 1: Oncology

Condition:

- Sub population of a haematological malignancy with a distinct biomarker most common in geriatric patients, slowly progressive but no cure.
- Current treatment usually “watch ‘n wait” followed by standard chemotherapy, with modest efficacy.
- Treated in centres of excellence by limited number of specialist haematologists.

Technology:

- New technology shows promise in studies lasting 2 years based on biomarker response based on n=60
- Oral treatment, taken daily
- Data immature – MA granted in single indication on basis of a single arm study, with no randomised controls but historical data from the natural history of the disease suggests the treatment slows progression
- Median overall survival and median progression free survival not yet reached
- The patients are continuing to be followed with ongoing clinical trials and via a registry.

Hypothetical case study 2: Neurodegenerative disease

Condition:

- Rare inherited genetic degenerative disease, progressive – fatal genotype by early adolescence
- No current treatment options

Technology:

- New technology shows promise in small clinical study lasting 2 years based on surrogate end points n=12
- I.V. infusion, weekly
- Data immature – MA granted on basis of a single arm study, with no randomised controls and no studies verifying contraindications, or other possible indications (sex, age, etc)
- As a condition of the MA a further 2 year randomised control study must be performed to verify the clinical benefit.
- Medicine developer sets a high price for drug to cover extra liable risks

Hypothetical case study 3: Very rare inherited paediatric disease

Condition:

- Disease has 4 different subtypes with the first subtype being very rapidly progressive to the 4th type being more slowly progressive. Patients do not survive beyond the 2nd - 3rd decade.
- Potential therapies should be initiated as early as possible, even at birth pre-symptomatically (before knowing the subtype) to prevent irreversible neurodegeneration. There is no disease modifying treatment

Technology:

- Gene therapy technology developed to address all subtypes of the disease. One time administration
- Single arm study performed in a subpopulation of children at a particular developmental age. Data compared to the natural history.
- MA/access restricted to the pivotal study population i.e. excludes very young children and older children.
- Additional studies are extremely complex because of the small number of patients and phenotypic variability
- Limited long-term safety

Part 2 – Additional scenarios to be explored under each case study

- The MA has been granted on a small cohort, with a positive benefit: risk
- Should patients be able to receive this medicine only if they agree to safety and efficacy data being collected (PV)?
- Should consent for treatment be obtained or mandatory?
- What happens to patients who decline to have extra data collected, or agree then change their mind?
- Reimbursement has been agreed in France but not in the UK.
- Should patients be allowed to travel to get treatment and how does that impact data collection?
- After 2 years, it becomes clear that there is a 3% incidence of a cardiomyopathy with heart failure. Many patients who are on treatment are happy and doing well. The pharma company wants to consider withdrawing from the market.
- Can a company be legally forced to maintain supply?
- Should patients be allowed to continue treatment? Whose decision is it?
- Can a patient who develops this Adverse Event seek compensation, and if so, from who?

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