

Medicines Adaptive Pathways for Patients (MAPPs)

A report on ethical issues, real world data and the views of patients and professionals by the Centre for the Advancement of Sustainable Medical Innovation (CASMI) on behalf of the Office for Life Sciences.

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Executive Summary

Medicines Adaptive Pathways for Patients (MAPPs) is a new, more adaptive approach to medicines development being discussed and piloted by the European Medicines Agency (EMA). The UK Department of Health (DH) and its Office for Life Sciences (OLS) asked Centre for Advancement for Sustainable Medical Innovation (CASMI) to investigate the ethical implications of MAPPs and explore the views of patients and professionals about the opportunities and challenges it may bring. The project was undertaken via a series of workshops and interviews conducted during 2015.

Although this work centres on the MAPPs process, it is highly applicable for similar early access schemes (i.e. Early Access to Medicines Scheme and Commissioning through Evaluation), the future Cancer Drugs Fund framework, and the Accelerated Access Review.

Ethical Considerations

No ethical implications related to MAPPs have yet been identified in the literature. This is a reflection of that the fact that this is a very new and rapidly evolving field.

Work done for this project identified key areas of ethical considerations that should be considered for each possible MAPPs approach employed. These are categorised according to: overall approach, thresholds of evidence, consent and research and monitoring.

Generalisable conclusions cannot be made given the challenges and the complexities of the issues under consideration, and the requirements to consider the ethical implications specifically for each MAPPs case. However, a number of issues warranting further work were raised, including the principle of equipoise (equal treatment of all patients once evidence is available) and how it applies to MAPPs; the implications for consent and potential therapeutic misconception (blurring the boundary between research and clinical practice); and the ethical issues raised through practical implementation of a MAPPs approach, such as enabling patient access and managing data.

Patients' perspectives

The majority of workshop participants expressed strong support for the MAPPs approach, especially in disease areas that were rapidly progressing and life limiting. Patients saw the MAPPs approach as potentially enabling them to have more control over decision-making, including more freedom to make individual choices about the level of risk they want to take on.

Participants reacted positively to earlier access, enhanced monitoring, earlier engagement in dialogue and in the design of treatment / research and a more joined-up approach throughout the lifecycle of a medicine, from research to reimbursement.

Notwithstanding, some significant areas of concern were raised, in particular around study design, communication and consent and data privacy / protection.



Fundamentally, an approach such as MAPPs will require early dialogue and engagement with patients, and the participants strongly advocated this. The approach needs to be tailored to the individual needs of the disease and the patients. Clear and concise communication will be necessary to ensure trust and transparency and to cultivate widespread understanding and support for the MAPPs process.

A major concern of patients was the integration of pricing and reimbursement discussions into the MAPPs process. Participants highlighted that on-going access to drug after the conditional approval phase of MAPPs would be a major concern when individual benefit was perceived; a situation where a drug was perceived to be working but would not be reimbursed would be seen as unacceptable.

Lessons to date from the EMA pilot

Enthusiasm for introducing a MAPPs approach is high amongst all stakeholders in the UK, although there is a great deal of concern about available resources to enable its introduction and about the appropriate pricing and reimbursement structure.

Regulatory tools that are already in place are being used to facilitate the MAPPs process as part of the EMA pilot. Given the fact that drug development requires a global approach to be commercially viable, regulatory approaches that are not applicable in other countries are likely to have limited appeal for industry. This is reflected in the numbers of expression of interest received for the EMA pilot study versus the Medicines and Healthcare Products Regulatory Agency (MHRA)-National Institute for Health and Care Excellence (NICE) joint scientific advice and the Early Access to Medicines Scheme (EAMS) initiative, both of which are UK-specific.

The pricing and reimbursement arrangements associated with MAPPs are still to be addressed however, and this uncertainty causes hesitation to engage in the process by all stakeholders. Identifying a payment structure that could be openly shared with all stakeholder groups would offer a great deal of reassurance to all that are currently hesitant to engage. This is not to imply that a commitment should be made on the actual price to be paid, but more of an agreement on the process that would be undertaken, the type and level of data required, and the payment structure to be considered.

Overall, it was agreed that pricing and reimbursement is the major hurdle to be addressed to make MAPPs a success in the UK.

Real World Data

Despite the UK and the NHS being globally renowned as a leader of healthcare data collection and utilization, the MAPPs process introduces new challenges. With a decision process on safety, efficacy, effectiveness and reimbursement made much earlier than in the normal pathway there is a much greater reliance on data collection outside of conventional randomized control trials (RCTs) (i.e. Real World Data (RWD)). There were major concerns from all stakeholders over the quality, quantity and ultimately reliability of this type of data

to make a meaningful decision during the MAPPs pathway, at a point where uncertainty was naturally higher. Open and ongoing communications around patient consent, data sharing and data security were deemed pertinent. Concerns from healthcare professionals on the current landscape were the intrinsic limitations of interoperability and data linkage of patient level data both intra and inter NHS trust and between academic and research entities. This results in time, resource and expertise burden beyond current capabilities. Regulators, payers and Health Technology assessment Agencies (HTAs) expressed greater concerns for applicable frameworks over minimal data standards, data access, data ownership and data costs. With RWD collection requirements and duration likely to vary by disease, geography and technology (i.e. a few months vs a few years), who would ultimately pay for the RWD collection if it extends beyond the normal timeframe of an RCT, is a question that remained unresolved.

Limitations of Work

This work provides an insight into the views of many stakeholder groups, and draws their views into one collective summary. Although the number of participants may be relatively small, and covering a small time-period, the depth of experience by those that participated, and the in-depth discussions achieved across a range of professional background and personal experiences (e.g. diseases covered) provides valuable insight. There was a clear and consistent message coming across from all that a MAPPs approach is worth pursuing, but that the process needs to be transparent, clearly communicated and engage all stakeholders, including those responsible for agreeing pricing and payment.

Summary of Recommendations

1. Building on the general ethical considerations identified in this work, product-specific ethical implications will need to be considered, in conjunction with ethics committees, to ensure positive adoption of a MAPPs approach.
2. Patients and patients' groups must be engaged very early on in the discussion, with clear and concise communication in place to ensure trust and transparency. This early dialogue will be essential to ensure widespread understanding and support for MAPPs.
3. Regulatory requirements and options are primarily in place, and should be adopted with a responsive, flexible and global, not national view in mind.
4. In order to make the UK an early adopter of the MAPPs approach, urgent efforts are required to address reimbursement, pricing and drug access. These are critical for confidence that MAPPs is a worthwhile route. One approach is conditional reimbursement alongside data collection, as explored in this report and through the work of the AAR.
5. Champion the importance and value of RWD as a decision tool for safety, effectiveness and reimbursement, engaging all stakeholders.
6. Place the UK at the forefront of EU initiatives that encourages early access of products.

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Chapter 1: Background

The last 18 months has witnessed a stream of activities in the UK and across Europe in promoting efforts to deliver drugs to patients sooner, saving time, saving lives and potentially also saving R&D costs. Prominent among these is the European Medicines Agency (EMA) announcement of ‘adaptive licensing’ pilots, subsequently termed Medicines Adaptive Pathways for Patients (MAPPs).

The Office for Life Sciences asked CASMI to engage patients in order to ascertain their views about MAPPs, to identify ethical issues associated with such revised approaches, and to assess the current landscape of real word data initiatives. Subsequently CASMI would advise on how the UK could lead in the implementation of MAPPs.

CASMI and its role and scope in this project

The CASMI team consisted of Deputy Director Megan Morys, Stuart Faulkner, Suzanne Ii, Liz Morrell, Fellow Sian Rees and Associate Elin Haf Davies, under the direction of Prof. Richard Barker. The original work plan involved preparing, convening, running and summarizing workshops with ethicists, patients and MAPPs stakeholders, in three work



streams. The proposed work stream 2: 'Brainstorming sessions with key individuals to provide options for reimbursement and incentive structures' was superseded by work done under the AAR. It was therefore later replaced with a new work stream assessing the 'Implementation issues of RWD collection'. Thus the three work streams reported on here are as follows:

- Work stream 1: patient engagement – a programme of focus groups and online engagement with patients and the UK public to assess attitudes to MAPPs, key concerns and best communication strategies
- Work stream 2: briefing key UK stakeholders on the latest MAPPs developments in Europe
- Work stream 3: qualitative interviews with key stakeholders assessing implementation of RWD collection relating to early access schemes, building on themes identified in work streams 1 and 2

The following deliverables were subsequently agreed:

- Patient engagement programme to research patients' attitudes and preferences and to design a) a list of considerations to feed into MAPPs project designs and b) recommendations of how to engage patients and the public in future.
- Discussion groups with selected individuals representing payers, NICE and companies focused around issues in relation to EU/UK regulatory opportunities and reimbursement models
- High level landscape of current RWD initiatives in England and recommendations of changes that need to occur to support early access schemes.
- Recommendations to DH, NICE and NHS England on how to maximize the likelihood of UK offering an attractive environment for MAPPs.

What is the MAPPs process?

Current processes for developing medicines are costly, complex and necessarily tightly regulated. Society is grappling with how to make the process faster whilst maintaining adequate controls to mitigate risks to patients and costs for healthcare systems. The standard route to demonstrating the safety and efficacy of a drug, and ultimately to lead to a Marketing Authorisation (MA) is based on a series of RCTs; clinical research conducted under controlled conditions and in tightly defined patient populations. While the 'gold standard' of clinical evidence, results from RCTs can differ from those seen when a drug is introduced into routine clinical practice and into a broader patient population, who may have co-morbidities and may be taking other treatments.

Alternative regulatory approaches to the standard licensing route are already available and are being used in a small number of cases. Conditional approval is one example, in which greater uncertainty about the risks and benefits of a drug can be tolerated. This may apply if there is no existing effective treatment, or when full RCT-based approaches cannot be successfully implemented, as is the case for some rare diseases.



Mechanisms for tracking outcomes from therapy (e.g. electronic medical records and patient registries and databases), mean that more 'routine' use of medicines in clinical practice can contribute to building a fuller picture of their efficacy and safety than is available from RCTs alone. This is referred to as 'real-world data'.

'Adaptive licensing' (AL) is a planned approach to progressive licensing of medicines based on utilisation of the conditional licensing route. It makes an iterative assessment and management of benefits, risks and uncertainties¹. It is increasingly being termed MAPPs, to emphasize the overall pathway and its potential benefits to patients.

European Medicines Agency (EMA) Pilots

On 19th March 2014 the EMA issued an invitation to pharmaceutical companies to submit potential candidate drugs to an adaptive pathways pilot project². Participation in the pilot is voluntary, and not considered binding: 'safe harbour' discussions are held without prejudice for the subsequent pathway chosen. The pilots will primarily utilise existing tools enshrined in EU regulation³ such as Exceptional Circumstances, Conditional Approval. The pilots may also incorporate risk management plans and other provisions of the pharmacovigilance legislation, such as post authorisation efficacy studies. MA would be an iterative process as more evidence becomes available, and not based on one single time-point of available evidence and data.

Under such a 'conditional' MA, approval for use of the drug is granted based on preliminary evidence of safety and efficacy. The sponsor company would be legally obliged to submit on-going data at regular intervals, with an obligation on the prescriber to undertake more intensive monitoring or to collect and share data regarding patient wellbeing. This would be considered as real-world data.

European legislation has recently developed to enable post-marketing efficacy studies to be mandated by regulators⁴. Such studies were previously not legally obligated and were frequently not undertaken⁵.

In current practice the sponsor company plans the development pathway, informed by responses to specific questions obtained through fee-for service scientific advice from regulatory and health technology assessment organisations. In contrast, the EMA describes the 'safe harbour' for MAPPs planning as an exploratory dialogue involving key stakeholders, as follows:

"Giving due recognition to the fact that discussions on possible AL pathways of a live asset are of an exploratory nature, interactions between stakeholders will take place in a safe harbour environment so that strengths and weaknesses of all options for development, licensing and assessment may be explored openly and discussed without fear or favour in advance of more formal interactions that might eventually be undertaken such as Scientific Advice / Protocol Assistance or Marketing Authorisation Application; this is to ensure that none of the stakeholders represented at the table will be asked to make binding commitments or suffer unforeseen consequences".



In order for a pilot to proceed, EU member states will need to volunteer to participate as “rapporteurs” for the pilots. The UK voiced a commitment to support such a pilot with an endorsement by the Prime Minister⁶ and the UK Expert Group on Innovation in the Regulation of Healthcare.⁷

The MAPPs approach is intended to extend beyond regulatory approvals, and into reimbursement, by means of engaging all relevant stakeholders - patients, clinicians, managers, industry, regulators, and payers (health technology assessments (HTAs)). Each participates in planning the research and monitoring needed to gather the evidence needed by all relevant agencies. The concept also includes restricting initial access to the medicine to those patients most likely to benefit, to accumulate evidence on the performance of the medicine in those patients and then to consider broadening the license to a larger patient population.

The MAPPs concept requires stratified medicine tools to define patient populations likely to respond best, and a data infrastructure capable of identifying these specific groups of patients and tracking the impact of specific medicines on their health. This is important to progressively reduce the level of uncertainty about the benefit-risk profile over time.

In summary, it is anticipated that a MAPPs process should:

- Enable earlier access to treatments than is possible under the current system, particularly for those conditions where there are few effective treatment options or there is unmet clinical need;
- Collect safety-efficacy data in ‘real’ patient populations, providing information that will help better target the treatment to sub-groups of patients who will benefit most, and a progressively greater insight into risk/benefit;
- Allow reimbursement while the levels of uncertainty are being reduced;
- Reduce development costs and risks (including late stage failures in total disease populations).

An overview of the EMA pilot scheme: selection criteria and proposals submitted

The criteria for acceptance onto the pilot scheme are:

1. Iterative development plan
2. Use of real-world data
3. HTA involvement

In addition, proposals need to have a sound pharmacological basis, and address areas of unmet medical need. Proposals were accepted for the pilots on the basis of the potential to derive broader learnings about the MAPPs concept and its implementation.

There has been strong uptake by industry. At the time of this project, 59 proposals had been submitted to the EMA for consideration (7 still to be assessed); 20 have been selected for further in-depth discussion of which 11 have been selected for stage 2 discussions.



Areas covered by the proposed medicines included asthma, cancer, advanced therapies, plus five orphan designations for areas of high unmet medical need.

EMA pilot: next steps

In terms of next steps, the EMA wish to have a number (11 are at 'in-depth' discussions with 2 at the 'safe harbor' stage) of Stage 2 discussions and formal parallel EMA/HTA advice procedures and then make a judgment as to whether continued learning can be achieved by continuing the safe-harbor discussions.

The Medicines and Healthcare products Regulatory Agency (MHRA) initiative

The UK has also introduced a scheme to address the need of getting faster patient access to drugs. An [Early Access to Medicines Scheme \(EAMS\)](#) was introduced in the UK in April 2014. Under the scheme companies voluntarily apply to have their early evidence on a new medicine assessed by the MHRA. If the MHRA believes that the product is particularly promising, with an acceptable benefit/risk profile - and with plans to manage risk in place - they will provide early guidance to help doctors and their patients decide whether to use the product before it is formally licensed.

The first stage of EAMS is for companies to apply for a Promising Innovative Medicine (PIM) designation. Companies need to have had a pre-submission meeting with the MHRA to discuss the application, fill in the application form, provide a summary of the pharmacovigilance system master file, and a Risk Management Plan using the MHRA template. The first full EAMS positive scientific opinion was granted in March 2015 to MSD's Keytruda (pembrolizumab) for advanced melanoma. The opinion spells out the evidence base, the benefits and risks and the approach to managing risk in early use in a Public Assessment Report. It also includes a treatment protocol for healthcare professionals, for patients and more detail on the pharmacovigilance system.

On the 8th Dec 2015 the MHRA website announced that a total of 18 PIM applications had been received, 13 granted and of those 9 scientific opinion applications received and 5 granted.

Interest by the pharmaceutical industry was initially low, evidenced through the small number of submissions compared to the EMA adaptive pathway initiative. When the scheme was launched it was thought that muscular dystrophy and dementia, alongside cancer, might be therapeutic areas to benefit. Since then, the MHRA has published a case study in December 2015 demonstrating that ~500 patients have subsequently benefited from early access to MSD's pembrolizumab. However, it is not yet known how interest in, and submission numbers to the scheme, will affect patient access in the UK in the long term.

Reimbursement appears to be a significant barrier to EAMS, as the sponsor is expected to provide the product at no cost to the NHS. Despite the benefits of securing early use the unknown risk of future reimbursement and revenue flow is undoubtedly causing hesitation in industry. This work is currently being explored under the Accelerated Access Review.

Chapter 2: Ethical Considerations

Methodology

A three-hour workshop to discuss these ethical issues was held at the Saïd Business School on May 27th 2015. A list of participants can be found in Appendix 1.

The workshop format began with a presentation by two CASMI representatives, followed by a discussion of around five or six specific questions in mixed groups of around eight participants, with plenary feedback to follow.

Background

A literature review conducted prior to the workshop did not identify any publications on ethics that explicitly used the terms ‘conditional’ or ‘adaptive licensing’. There is discussion in the literature on ethics associated with the traditional regulatory route and research process, including Phase IV trials. For example, the circumstances that justify the exposure of patients to risks in the context of RCTs. There is also a body of work relating to the moral concepts associated with access to untested treatments for terminally ill patients for whom usual treatments do not work^{8 9}, for example relating to rights and individual liberty.

A key underpinning issue that may need further debate is an individual patient’s right to access experimental (non-licensed) treatments versus the societal need for access to be granted (via marketing authorisation) only on provision of robust evidence of safety and efficacy which is generally accepted to only be available on completion of trials¹⁰. For the purposes of this workshop however, discussion was restricted to exploring whether conditional pathways and adaptive licensing create ethical considerations that are wholly, or subtly, different from standard licensing and research pathways.

Issues arising from the workshop

Under adaptive pathways the drug may be granted a conditional approval, with a greater level of uncertainty about its risks and benefits than is usually the case and so either further research or greater observation is needed. In this situation the normal distinction between the research and therapy phases becomes blurred; some patients will be being prescribed the drug as part of on-going research and some as part of routine clinical practice. Bringing research closer to usual clinical practice is clearly desirable from the perspective of science as the results of any trial should be more easily generalizable.

However, it raises a number of issues. These were defined in this work as:

- The nature of evidence needed for early licensing,
- Issues of consent,
- The nature of post-approval monitoring and research, and
- The implications of findings from such research.

This places responsibility on those participating in pilots and subsequent practice, particularly those representing patients and acting as agents for the health service, to ensure that the proposed development plan and patient access is ethically sound.



Three overarching ethical considerations to be reflected upon when considering the suitability of introducing MAPPs are listed below. These should be considered each time a MAPPs approach is to be implemented.

1. Do the ethical dilemmas posed by MAPPs differ from those associated with current processes?
2. Are there types of therapy or circumstances in which MAPPs is not appropriate on ethical grounds?
3. Given the ethical issues identified, are the concerns with the existing regulatory system (for patient, delayed access and for instances the cost and time challenges associated with some treatments) justified, and the safeguards proposed sufficient to support the MAPPs proposals?

Thresholds of evidence for MAPPs

It is unclear whether it is possible to establish in general terms the 'level of evidence' that would be required for a conditional approval to be granted, for example a 'large' Phase II study. In reality this may vary from case to case depending on the nature of the disease, the characteristics of the drug and the evidence that has been collected.

As a result of the limited initial data about the drug and its effects at the time of conditional approval, there is a greater level of uncertainty about its benefits and potential harms. The issues this limited level of data raises that must be considered are listed below:

- In what circumstances is it ethically permissible to expose patients to this drug as part of clinical practice - for example only if they are included in a register or as part of a full clinical study?
- Should the drug only be prescribed by those with specialist expertise in research and the use of innovative drugs? Does this mean some patients might not be able to access the drug, introducing 'postcode prescribing'?
- Should patients be more closely monitored than would be usual in clinical practice to ensure that all risks and benefits are identified?
- Can licensing conditions be enforced to prevent premature off-label prescribing, given the clinician's 'therapeutic privilege' which protects their professional autonomy in common law to treat in the best interests of the individual patient?
- Could this create a greater imperative/pressure for clinicians to perform research after licensing? Arguably this would be for the public good; however the existing pressures on healthcare systems and clinical staff are widely acknowledged.



Consent

Under the current conditional approval arrangements drugs can be used as part of routine care and, unless stipulated in specific cases, there are no general regulatory requirements for any enhanced monitoring.

If it is agreed that as part of a MAPPs framework arrangements need to be made to address the increased uncertainties around risk/benefit there are a number of options:

- the patient receives the drug as part of clinical practice with enhanced monitoring
or
- the patient can only receive the drug as part of one of the planned clinical studies.

Both options introduce the potential for the patient to be unclear about whether they are participating in research, with its attendant protections, or not. This misunderstanding has been described in the literature as ‘therapeutic misconception’¹¹. This is also observed in traditionally designed trials in which there is restricted or no access to those treatments that would have been rationally preferred. Therefore, if it is indeed an issue, it is likely to be one for both standard and adaptive routes. This might also lead to a perception that patients are being coerced into research participation to gain access to the new drug, again a problem for research under traditional licensing schemes. These are empirical questions, which could only be answered through proper survey of patients for the specific products in question and a parallel review of the current definitions of research consent.

This places a clear duty of care for the clinician to explain the uncertainty surrounding a conditional license and an obligation on the system to ensure the materials are provided to support those discussions.

Three key considerations to be kept in mind regarding the ethics of consent are listed below:

- What safeguards/communication materials need to be in place to ensure that patients are fully informed and ‘therapeutic misconception’ is avoided?
- To avoid coercion, are there any circumstances in which patients should be allowed to access the drug without their data being collected? Or do the potential risks and uncertainties prevent this being a possibility even if safeguards can be put in place to ensure patients fully understand those risks?
- Will informed consent introduce unacceptable bias into the results of trials as certain groups of patients may refuse consent?

Research and monitoring

A key element of the adaptive licensing proposals is that all stakeholders participate in co-designing the development plan during the safe-harbour phase. The development plan will presumably include an exploration of the types of monitoring and research expected and whether preference trials or cohort studies will be conducted (although it is still unclear



under what circumstances they could be submitted as evidence to regulators and payers). Standardization of any data collected will be needed to ensure that it is usable for monitoring.

In the context of medical research it has been argued that it is only ethical to randomize patients to different treatment arms under conditions of equipoise – namely genuine uncertainty about which option is best. It helps to ensure that all arms of a trial are consistent with competent medical care and research ethics committees should take equipoise into account. Once evidence has accrued and indicates that one treatment is superior, that treatment option should be offered to all patients (assuming resources are available).

Equipoise therefore requires two things: (1) a state of uncertainty or disagreement in the community of expert practitioners over the merits of various interventions and (2) that a trial be designed in such a way as to make it reasonable to expect that, once the research is successfully concluded, its results should be convincing enough to resolve the dispute among clinicians.

There is debate in the research ethics literature over the most appropriate interpretation of equipoise and about its general utility¹². There is also debate in the literature as to whether the threshold for equipoise lies at the point that the individual clinician is convinced of the effectiveness of the drug or that the drug is deemed accepted by the research and/or clinical community more broadly^{13 14 15 16}. With respect to adaptive licensing, despite there being sufficient information on which to grant a conditional license, the preliminary nature of that evidence means that the drug may still be harmful or ineffective, in itself or compared to other treatment options.

Conditional licenses (including those under exceptional circumstances) can only be granted in a number of specific circumstances (well-defined patient populations, high unmet clinical need and benefits of immediate availability outweighing the risks inherent in incomplete data). The implication is that this is anticipated to be for relatively small groups of patients. It may be anticipated that relative effect sizes may be larger than normal, for example because there is no viable alternative. It may also mean that there is a smaller patient group and therefore trial recruitment may be difficult.

The ethical issues are compounded by the fact that the patient may be randomized to either placebo or an existing treatment that may not have previously worked for them. Where this is a life-threatening or life-limiting disease, as with most drugs receiving a conditional license, the potential for this to happen will undoubtedly not be acceptable to the patient and will potentially compromise the research. This is particularly the case when the patient has only agreed to the research in order to get access. Therefore, different research designs may be required.

Points to be applied when considering the ethics of study design and monitoring are listed below:

- Are there any research designs that are ethically preferable to others? Are there any that should not be considered?
- Is there a greater imperative to collect data for research purposes after conditional licensing?
- Should individual patients be allowed to make this decision or can patient groups adequately represent the interests of those patients?
- How does the concept of equipoise apply in the context of adaptive licensing? Given the fact that there is sufficient evidence to grant a conditional license does this mean that there is no longer equipoise?
- If there is sufficient information to enable a license to be granted is it still ethically possible to conduct placebo-controlled trials to gather further evidence of efficacy?

Summary of recommendations linked to ethical implications

General ethical considerations have been identified in this work, however specific ethical implications need to be considered in more detail.

Although each approach will need to be considered in isolation linked to the disease presentation and the relative risk benefit, some more detailed general principles can be developed.

Further work to be considered would be a review of ethics committee members to understand their interpretations of the implications. Understanding the likely concerns that may arise may help to prepare for addressing for these in advance. This would be particularly important to ensure positive adoption of such approaches across various ethics committees in the future.

Contributors to the ethics work

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Chapter 3: Patient perspectives

Design of workshops

Three separate workshops were organised to allow for a wide insight into patients' views across different diseases, in terms of severity and rate of progression:

Workshop 1 - patients (and carers) with chronic adult onset diseases – in particular Alzheimer's and Parkinson's disease.

Workshop 2 - patients (and carers) with life limiting adult onset disease – in particular motor neuron disease (MND) and myeloma.

Workshop 3 - parents of children with life-limiting diseases – in particular neuronopathic Gaucher Disease, Duchenne muscular dystrophy, brain cancer and Niemann-Pick Disease type C.

Patients were identified and recruited via patient support groups. The work was approved by an Ethics Committee in Oxford University. Each participant signed a consent form to take part, and allowed the workshop to be voice-recorded, and for their views and opinions to be incorporated into this report under the Chatham House rule.

Each participant received a briefing note prior to taking part in the workshop and a list of open-ended questions to guide the discussion was developed beforehand.

An independent moderator was appointed to facilitate each workshop, with two members of the CASMI team also attending each. Each workshop started with a presentation of the current drug development pathway, and an introduction to the MAPPs pathway. The moderator was then given a list of open-ended questions to seek the views of the participants, about the advantages and disadvantages of the current system and about the possible risks and benefits of the MAPPs system.

Each workshop was voice-recorded and transcribed. Each CASMI member summarized the discussion for the workshop for which they were responsible, and then the findings from each workshop were integrated to common themes across all three. The summary of each workshop was also shared with the relevant patient groups with a request to provide comments.

A total of 20 participants took part across all three workshops. Although the total numbers can be considered relatively small, the process covered eight very different diseases, varying in presentation, progression and severity. The group also included both patients and carers (parents and partners). The small number in each group allowed all participants to have sufficient time to reflect and contribute meaningfully.

Workshop 1: Chronic adult onset disease [Alzheimer's and Parkinson's disease]

Brief description of participants

The first workshop was held in London at the Headquarters of Alzheimer's Society on the 14th of May 2015.

Workshop participants included five people with Parkinson's Disease, with varying lengths of time since diagnosis, a carer of someone with dementia and a person recently diagnosed with dementia.

Participants were recruited through an open invitation to:

- Members of Parkinson's UK Research Support Network and
- Alzheimer's Society London Network

Comparison of MAPPs with current process: benefits, risks and perspectives

Considerable discussion took place about the nature of the current process and how MAPPs would differ, indicating the need to ensure such basic understanding when eliciting patient views. In fact, background knowledge and understanding varied amongst participants: two had been participants in clinical trials, and one expressed several concerns about taking medication or being involved in trials or MAPPs. Other observations of relevance and interest were:

MAPPs was identified as an opportunity to address some of the issues in the current system, in particular:

- There was a general agreement that the current process is too slow and that being involved in trials or MAPPs may be for the benefit of others.
- Participants felt that the current process could be improved by reducing waste in the system, increasing trial size and recruitment effectiveness through the use of technology, and increased repositioning of existing treatments.
- A key question was how much time would in practice be saved if MAPPs were introduced?
- MAPPs might be suitable for people with life-limiting conditions where current treatments are limited.
- Considerable concern existed in this group about lack of current treatment options. There was seen to be a trade-off between symptom control and side effects.
- Worries were expressed about the risks (and whether these compared to those associated with well-publicised cases such as thalidomide and the Northwick Park trial, where healthy volunteers developed organ failure).
- There was universal agreement that choice as to whether to take any drug should be the individual's, based on full discussion of the known benefits, risks and side effects and what uncertainties remained. An individual's capacity to make decisions, the stage and severity of disease, and the acceptability of current treatments all inform decisions about how much risk an individual might take.

The more severe the disease the greater risks are likely to be acceptable. The prospect of a cure or significant improvement e.g. *'getting out of a wheelchair'* were thought to mitigate increased risk. There was considerable agreement that improved quality of life might be an acceptable trade-off against length of life.

- The severity of potential risk is also important in making decisions, and different risks might be more or less important depending on individual fears and worries.
- A concern was expressed that MAPPs is part of the agenda of pharma companies and profit might be a motivator. Concerns were expressed about trials run by industry, with more faith being placed in independent medical professionals. However, for some patients, the medical professional might be seen to have disproportionate influence over them.

Key considerations for designing a MAPPs process

The group were asked for their input into MAPPs process design:

- There was considerable agreement that patients should have input into any new process for licensing, with a clear definition of principles/criteria and a desire to understand who would coordinate the plan.
- There was a desire to understand how many people needed to be in effective trials under a MAPPs process. (There was a comment that a Europe-wide approach might be better as it could include more people.)
- Pre consenting process was discussed, including the value of a register of people willing to be contacted as potential trial participants and/or open to being prescribed a MAPPs drug. In cases in which the patient's decision power was diminished, it was felt important that their wishes be included in lasting power of attorney or in living wills, perhaps held by charities.
- There was no consensus on whether off-label prescribing should be allowed.
- A single point of contact for patient was thought important, given variable knowledge amongst professionals, including a lack of very specialist knowledge in general practice, especially with relatively rare diseases. (GPs need to know what is happening, but there was general support that the key point of contact should be with a specialist.) It was important to recognize geographical variation in service provision (e.g. availability of Parkinson's nurses).
- There was a worry that if the drug failed in the overall group, it would be taken away from those patients where it had proved beneficial. (Or could a drug company be obliged to continue providing a drug for those that have benefited?) In such a case, would the drug go into a phase 3 trial?

Workshop 2: Life-limiting adult onset disease [motor neuron disease (MND) and myeloma]

Brief description of participants

The second workshop was held in Birmingham at the Birmingham Medical School on the 30th of April 2015. All invited participants were people with motor neuron disease (MND) or myeloma.

Workshop participants included seven people with MND, one accompanied by a husband and carer, one by a wife and carer; and five people who had been diagnosed with myeloma, one accompanied by a wife and carer. Carers participated in the discussion. Most participants had been diagnosed from between one and three years ago; the longest had been diagnosed nine and a half years. Around half of participants had already taken part in a clinical trial and the majority said that they would do so if invited to in the future.

Participants were recruited through an open invitation to:

- Worcester Myeloma Support Group and
- MND Association

Comparison of MAPPs with current process: benefits, risks and attitudes

There was an agreement amongst the group that the current system doesn't work for people with life-limiting diseases, because the development and approval timescale is just too long. The system was described as being "*developed by institutions*" with a primary objective of reducing risk. Pharmaceutical companies are considered to be primarily 'covering their own backs'. The current system lacks flexibility and is one-size-fits all approach, and participants felt that it did not fit them and their disease.

MAPPs was identified as an opportunity to address some of the issues in the current system, in particular:

- To **speed up** the drug development process;
- To give patients and clinicians **more choice**, and more **freedom to make individual choices** about the level of risk they want to take on;
- To **involve patient groups earlier** in the development pathway and make drug development more patient-centric.

A concern was expressed that adaptive pathways might involve 'cutting of corners', making it harder to generate conclusive evidence of efficacy. Participants were very concerned that the integrity of datasets not be compromised and that we would still be able to tell if a drug was working or not, even if a formal placebo-controlled clinical trial had not been performed.

Participants commented on the pharmaceutical industry culture, in particular the need to be risk-averse (leading to limited risk-taking) and the commercial and competitive instincts of the corporate world. In particular participants advocated the use of collaborative models and shared data to avoid unnecessary duplication of effort.

Key considerations for designing a MAPPs process

Most participants noted that MAPPs is most likely to be relevant for conditions with small numbers of sufferers.

Participants wanted as much information as possible, but were also concerned that it be delivered in a way that enabled them to fully inform their carers and explain the risks

and benefits. Carers came across as a major stakeholder since both the risks and benefits also severely impact their lives.

Some participants thought that a MAPPs drug would be safe but uncertain in efficacy, whilst others had the impression it works but might have unintended consequences. Either way, they wanted the situation to be explained clearly with enough time to think through the trade-off.

Participants felt that MAPPs would naturally come with a higher degree of monitoring and that this was reassuring. A multi-disciplinary team of specialists would be needed. Ongoing feedback about the individual and the cohort (not just 'results at the end') was considered essential.

The group agreed strongly that patients on a MAPPs drug should be required to consent to the sharing of their data. Many participants were interested in trying new treatments not for themselves but to develop a cure for when their children or the next generation was in the same situation. They could not see the point of the pathway unless data was collected.

Participants reported that data collection should be simple and effective and that the data collection plan should be communicated up front, with transparency on with whom the data would be shared. (Anonymised data could be shared with many stakeholders, but personal data only with people caring for the patient.) Participants were more comfortable with 'the NHS' holding data than individual academics, who might be influenced by a company. Telemedicine was mentioned as a possible tool. Participants also noted that the outcomes measures needed to be more relevant to patients.

MAPPs was expected to be an adaptive and responsive process (similar to 'agile' thinking in software development) with feedback and iterations.

Participants described a number of negative experiences with general practitioners (GPs) who had not come across their condition before. They agreed that specialists – and ideally a team of more than one specialist – should be the prescribers of MAPPs medicines. There was some concern that this could lead to inequality of access across different regions, especially as some people whose condition is stable don't see their consultant regularly.

Participants felt that an increased responsibility for decision-making needed to come with appropriate emotional and physical support. The group could not agree on where that support should come from but a multidisciplinary team was called for.

There was a strong feeling that if the reimbursement pathway was not there, that would be ethically unacceptable to proceed – especially if an efficacious drug was withdrawn or not everyone was able to access it.

Participants were not concerned about public opinion or the Daily Mail interpretation of events, but strongly advised working with patient groups first so that there are advocates for the process among people who are benefitting.

Workshop 3: Parents of children with life-limiting diseases [neuronopathic Gaucher Disease, cancer, Duchenne's muscular dystrophy and Niemann-Pick C disease]

Brief description of participants

The third workshop was held in London at the Wellcome Trust on 6th May 2015. Invited participants were parents of children and young people with life-limiting conditions.

Workshop participants included eight parents (one father, seven mothers) of children with life-long or life-limiting illnesses including brain, head and neck cancer (1), neuronopathic Gaucher disease (3), Niemann-Pick C (2) and Duchenne's muscular dystrophy (2). This group of participants were extremely well informed, not only about the regulatory approval of drugs, but also the reimbursement procedures. Six out of the eight had consented to take part in a clinical trial, either currently or in the past.

Two of the participants also had direct experience of engaging in a regulatory procedure with the EMA, while another two had involvement with procedures for the reimbursement of drugs. Five participants were active with patient groups. One parent was also a GP.

Participants were recruited through an open invitation to:

- Gauchers Association UK
- Niemann-Pick UK
- Joining Jack Childhood Cancer

Comparison of MAPPs with current process: benefits, risks and attitudes

There was an agreement amongst the group that the current system does not function well to bring new drugs to patients, in terms of time required and in terms of the overall process used. MAPPs was therefore seen as a real opportunity to change things.

The opportunities aligned with those expressed in the second workshop:

- To **speed up** the drug development process timeline.
- To have **regulatory approval** and **Health Technology Assessment** review done **at the same time**.
- To have **patient group involvement** right from the **beginning** of drug development plans.

A potential benefit identified from introducing a MAPPs approach was that new and innovative study designs could be introduced, designs that would not require the use of placebos in life-threatening, life-limiting illness. Such approaches could then be widely promoted by the participants.



Another possible benefit identified was early engagement of all stakeholders **before** the initiation of any process, which could lead to a better understanding of patients' needs and views, and what data both regulators and payers need in able to make their decisions.

A risk expressed of adaptive pathways was that drugs of limited benefit might be approved, especially in complicated diseases where it is very difficult to show decisive evidence of efficacy. To combat this, there is a need for very robust markers and very good ways of collecting longer term data.

Participants expressed that drugs are currently being approved on endpoints that basically mean nothing to patients. Identifying a more holistic, patient centric set of outcome measures and means of monitoring would be a real benefit.

A perceived challenge expressed by the participants is that the pharmaceutical industry is very risk averse when developing drugs because there is a lot of money involved.

Drug access at the end of a MAPPs process was identified as a potential risk that would need careful attention, to avoid distressing situations where patients would not have continued access to a drug that they had found to be effective for them. A carefully planned up-front arrangement was considered necessary to ensure that the issue was well managed.

Key considerations for designing a MAPPs process

Respect for patients should be the cornerstone of any process, and especially in terms of the communication process. Information must be conveyed about the risk, benefits and uncertainty in the process of gaining informed consent, but also in terms of communication throughout the trial. Updates should be provided as often as they are available, as well as the results of analysis performed at the end.

There was an identified need to find the right balance between ensuring adequate monitoring of patients, without over burdening them with invasive tests and frequent hospital visits. Mobile and wearable technology might be one option to facilitate this.

There was a strong feeling among the group that data sharing should be an obligatory part of MAPPs, in order that the whole community can benefit. It was also considered essential that data-ownership should always belong with the patient and the patient group. Pharmaceutical companies should be forced to share any data they might hold, regardless of whether it makes them loose their competitive edge.

MAPPs was only considered to be a suitable option where there was significant therapeutic need, either from the lack of treatment options or of the risk of imminent death. MAPPs was not considered a suitable approach if only small, incremental benefits could be foreseen.

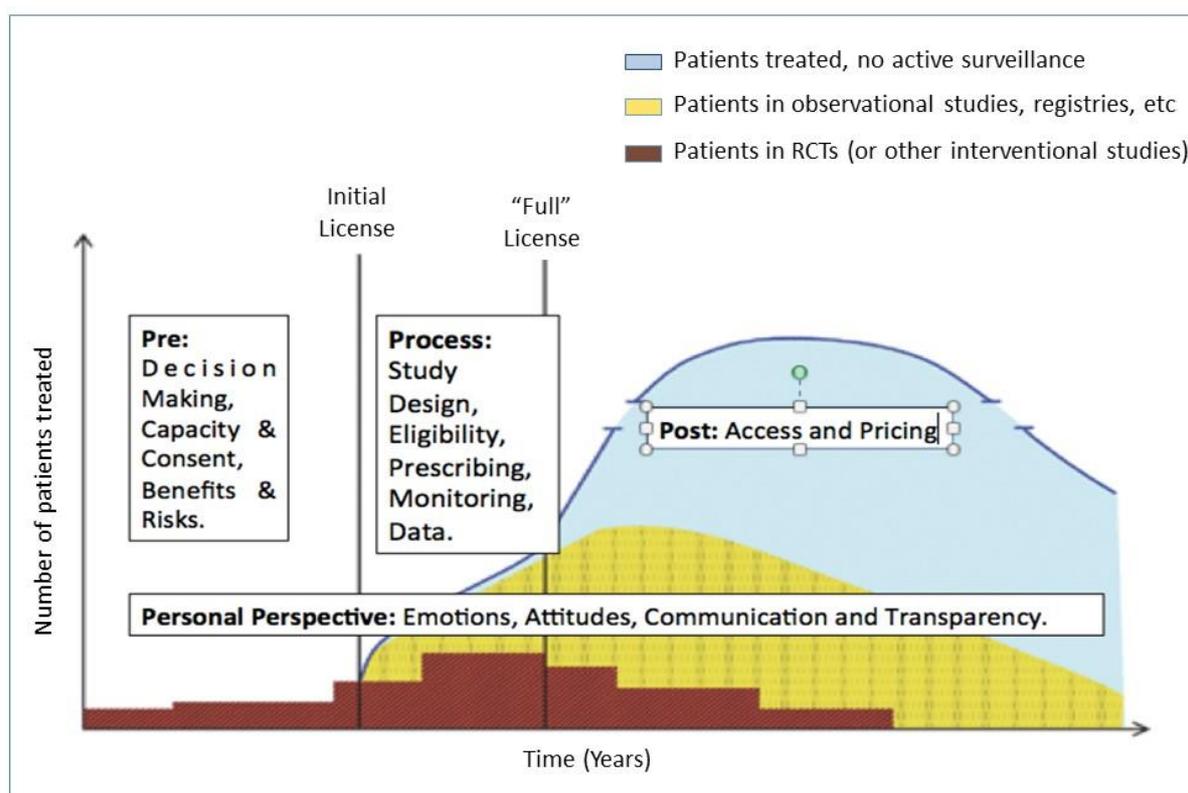
Common emerging themes from all three workshops

Twenty-six themes were identified in total from the analysis (presented in Appendix 2) of the transcripts of all three workshops. Four overarching areas were defined

according to the point at which these issues would most likely emerge in a MAPPs process (Pre, In-Process and Post). The fourth ‘Personal Perspectives’ includes themes that are important to patients throughout the MAPPs process.

1. **Personal Perspective:** Emotions, attitudes, transparency and communication.
2. **Pre MAPPs:** Decision making, capacity and consent, benefits and risks.
3. **MAPPs Process:** Study design, eligibility, prescribing, monitoring and data.
4. **Post MAPPs:** Access and pricing.

These aspects are illustrated and presented in more detail superimposed over each stage along the proposed MAPPs pathway (Graphic 1).



Graphic 1: The overarching themes of patients’ views illustrated across the MAPPs timeline. Adapted from: Adaptive Licensing: Taking the Next Step in the Evolution of Drug approval H-G Eichler et al, *Clin Pharmacol Ther.* 2012 Mar; 91 (3):426-37

1. Emerging themes linked to the personal perspective:

Four themes emerged of importance throughout: **emotions, attitudes, transparency and communication**. All four are considered integral to the complete MAPPs process, and impact on every step. This cannot be emphasised enough in terms of the support required to ensure the successful implementation with patient acceptance. These aspects are specified in more detail below, with an overview of some of the most relevant and poignant views expressed by participants linked to this theme are illustrated in graphic 2.

The detail of ideas emerged for each one is highlighted in Appendix 2.

**Illustrative quotes of the Personal Perspective:
Emotions, Attitudes, Transparency and Communication.**

'time is not on our side'
'Anyone who has got time's winged chariot coming-up behind them needs this.'
'If there's any significant risk or risk of side effects, then that should be communicated as soon as possible.'

'give us a greater voice'
'Faustian agreement with one's medication'
'everyone is different'

'make it much more patient centric again'
'...if you're asking patients to become involved in a process early you need to reward them a certain amount of respect...'
'need to be fully informed and fully aware'

'I would say nearly everyone is conflicted'
'lack a voice.'
'...what I would want to take part in a trial.... to be based on a report by the independent medical and research group who looked at the statistical information and the clinical information being touted by the drug company before the licensed trial.'

Graphic 2: The overarching themes of patients' views illustrated across the MAPPs timeline

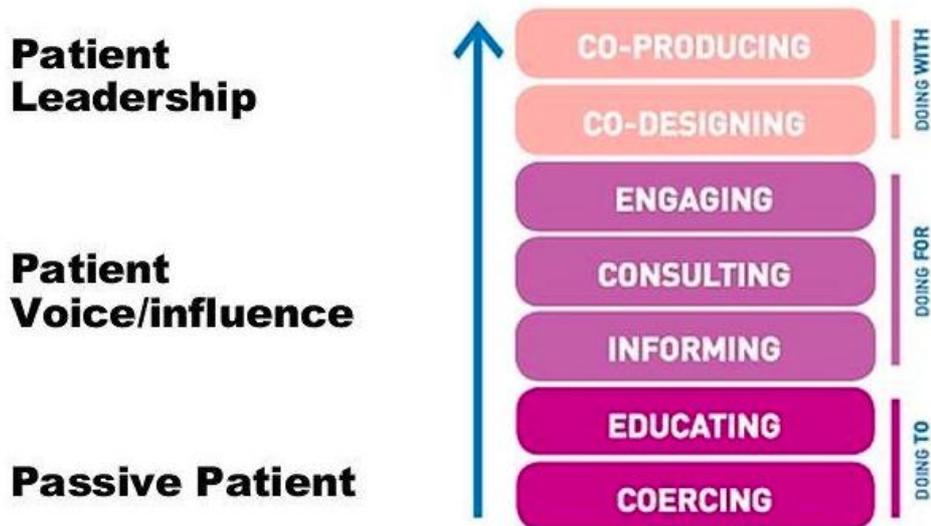
The main themes in this section were:

- The need to communicate respect and reflect this in open communication and the sharing of information throughout the process
- The recognition that patients (and carers) vary widely in their knowledge of the current process and the considerations involved in MAPPs
- The need for trust in both the process and the professionals involved
- A strong focus on the value of empowering the patient to be part of the decision making process right from its conception, moving away from the 'passive patient' model to a 'patient leadership' as illustrated in graphic 3.

2. Emerging themes related to pre MAPPs

Three sub-topics emerged under this theme, the **decision making process**, the **capacity and consent** required for such a decision and an understanding of the potential **benefits and risks** that would be undertaken. Further details of the issues that emerged are listed below, along with some of the illustrative quotes:

Where are we on the ladder?



Source: new economics foundation

Graphic 3: Moving from 'passive patient' to 'patient leadership'

**Illustrative quotes of the Pre part of the MAPPs process:
Decision Making, Capacity and Consent, Benefits and Risks.**

'we consider our generation are the ones that are trialing the drugs for the generations below us'

'Because taking part in a medical trial is a massive burden ... it's still a massive emotional burden not just on us, but on our children'.

'We maybe desperate but we are not stupid.'

'It's a risk and reward equation.'

'I'd be prepared to throw the dice, but I'd want to know what the potential outcomes risks and rewards are. That's not something we get at the moment'

'One of my daughters would never have put me near a trial, the other would'

Graphic 4: Illustrative quotes to represent themes associated with the pre part of the MAPPs process

The key themes were:

- An understanding that, for some patients, their motivation is gaining knowledge for future generations, rather than their own immediate benefit
- The need to explain in as much detail as possible, the potential for benefit and for risk, and the level of certainty/uncertainty
- The importance of a proper consenting process, reflecting the differences in the situations of patients with different diseases

More detail of ideas emerged for each one is highlighted in Appendix 2.

3. Emerging themes identified related to the MAPPs process itself

Five sub-topics emerged under this theme, the **study design**, to be used and the appropriateness of using placebo arms, patient **eligibility** required for such an approach, the **service delivery and prescribing** to support it and the **monitoring and data** aspects that would need to be considered and incorporated as part of such an approach, with a focus on **confidentiality**. This also included aspects related to data ownership and sharing. Further details of the issues that emerged are listed below along with a graphic illustration of some of the quotes:

Illustrative quotes of the Process part of MAPPs:
Study Design, Eligibility, Prescribing, Monitoring, Data.

'We all felt that the use of placebos was not an ethical trial option when treating patients with life-limiting diseases, although a 'no treatment' trial path (as exists now, and which I was randomised for) was more acceptable'.

'time is not on our side'

'Short trial and as broad a cohort as possible. Perhaps using the new technology and the smart watches, smartphones, etc. to monitor us'.

'The placebo is key, I would say. If you've got children with degenerative diseases, nobody wants to go on a trial for a placebo'.

*'If we had a regulatory body which also administered trials across European countries, with large cohorts of people, **monitored by active technologies**, I would feel much more confident about it than something which is run in Britain with 31 people from a small lab in Oxfordshire'.*

Graphic 5: Illustrative quotes to represent themes associated with the process part of MAPPs

The key themes were:

- Study design: the need to be flexible, and to avoid a placebo arm when this offered no potential for benefit. The Worcestershire Myeloma Support Group, in response to the summary for workshop two, expressed that *'we all felt that the use of placebos*

was not an ethical trial option when treating patients with life-limiting diseases, although a 'no treatment' trial path (as exists now, and which I was randomised for) was more acceptable'

- Patient eligibility: the need for maximum fairness and transparency in those able to participate
- Service delivery: the need to put the process in the hands of specialists and have them act as a single point of contact
- Data, monitoring and confidentiality: the need for patients to consent fully to data sharing (personally identified data only to the professionals caring for them)
- The detail of ideas emerged under each heading are in Appendix 2.

4. Emerging themes Post MAPPs

What would happen at the end of a MAPPs process raised significant concern for patients, particularly when considering the personal effort and emotion likely to have been invested in such an approach. The need for reassurance that their efforts and needs would be respected and recognized was high. Communicating the decisions at every single step along the process would be key. These are illustrated below along with illustrative quotes:

**Illustrative quotes of the Post part of the MAPPs process:
Access and Pricing**

'It's not even the difference between walking and not walking. It's life and death. It's scandalous'.

'At the moment, it's almost like there are two Mount Everest to climb...there's the regulatory hurdle and there's the reimbursement hurdle'.

'To me, having this process where you do HTA at the same time as getting regulatory approval, it sounds like a dream ticket.'

Graphic 6: Illustrative quotes to represent themes associated with the post part of MAPPs

The key themes were:

- The need for upfront agreement about reimbursement, without which the process makes no sense
- Reassurance that, in the event of a drug 'failing' overall, it could be continued for those patients for which it had proved valuable

The detail is contained in Appendix 2.

Comparing and contrasting the three workshops

The general feel of the workshops varied greatly between the first and the latter two. Participants of the last two workshops were generally more informed about the current clinical trial process and both the regulatory and reimbursement issues linked to drug development and patient access.

In the latter two workshops, which included participants with experience of life-limiting diseases, there was a general agreement that MAPPs was considered to be a great opportunity for patients. Overall, there was great level of agreement by participants in workshop two and three. This may be linked to the fact that the diseases in questions are rapidly progressing and life-limiting in nature.

Some participants in workshop one were more hesitant about the value of the MAPPs approach, and showed greater levels of anxiety about both the risks and a lower level of trust in the pharmaceutical industry. This could reflect the nature of their condition (longer term experience of therapy).

Conclusions and recommendations from the three workshops

Feedback from most participants during these workshops indicated that an approach such as **MAPPs would be greatly welcomed** by them, with the hope that it would save time, broaden patient eligibility able to take part and facilitate bridging the gap between regulatory approval and reimbursement.

Open communication and **transparency** was considered a crucial facet of MAPPs if trust were to be maintained. Patients repeatedly emphasized that the decision was an individual one to be made, and that with the **right level of information and support** it was one that they would want to be able to make themselves.

Data sharing is an issue that can be addressed by reassurance of anonymity, and an up-front agreement (and consent) on data sharing. Some patients felt strongly that data sharing **should be a social obligation** in exchange for access to the drug and/or on-going monitoring, but that all data should be publicly available / owned and not solely owned by one pharmaceutical company.

Monitoring needs require additional consideration with a **greater use made of digital health** and emerging technology. Patients report that they need the tools to be able to report their symptoms but also be able to receive up-to-date communication in real-time.

Patients with an experience of both regulatory and reimbursement issues expressed optimism that a MAPPs approach could be a solution to address this as 'one summit to climb', rather than two.

Patient participants did not report concerns about potential scaremongering in the media as long as they had been well informed before, during and after. This is in contrast to views of some of the professionals that attended the stakeholder group workshop (reported below).



Specific work that would benefit further exploration with patient groups would be on how best to communicate benefit and risk (NB an IMI project call on this subject has been issued, called 'Protect'). This work could involve the creation of patient information sheet templates and potential consent forms to be used.

Contributors to the patient workshops

- Megan Morys, CASMI
- Elin Haf Davies, CASMI
- Sian Rees, HEXI
- Katherine Cowan, independent facilitator
- Bec Hanley, independent facilitator

Chapter 4: Professional workshop - lessons to date from the EMA pilots and challenges to implementation

Methodology

A stakeholder meeting was convened on April the 27th 2015 to examine an interim summary of and lessons learnt from the EMA pilot scheme, and discuss the main challenges and opportunities for the implementation of MAPPs in the UK.

The discussion was held under the Chatham House rule, with representation from the following organisations: NICE, MHRA, NHSE, DH, GSK, the SME community, patients, and CASMI.

Professor Sir John Bell made a few opening remarks, and was followed by presentations from Rob Hemmings (MHRA/EMA) and Sarah Garner (NICE), summarizing their observations on the EMA MAPPs pilot scheme to date, and some lessons to learn (as presented in the background section). Industry representatives in the room also shared their experience of the pilot scheme during the discussion.

Themes emerging

Several themes emerged from both the presentations and the discussion:

- Everyone is learning together: there is a general willingness to explore the MAPPs pathway on the part of industry, despite some reticence by some of the large companies to submit proposals.
- Government bodies are also eager to engage.
- Notwithstanding that, there is a certain caution due to uncertainty over where the pathway will lead.
- The pilot was created with the limitation to use the tools within the existing legislation.
- The regulatory toolkit exists and is not overly complicated.
- The main source of concern is pricing and reimbursement: how will it work, who decides, and what will be the financial implications for all stakeholders?
- Proposals by industry in the pilot thus far have not been *'adventurous'* in challenging the traditional drug development pathway, particular around use of real world data (RWD).
- There is still some concern over the cost to the NHS and where the value comes from for the NHS.
- Involving patients and incorporating their views into the design of the pathway is important: could this be made a condition of entry?
- Securing the necessary real-world data (getting the right level and quality of data, suitable end points, quality control and practicalities) is also an issue which needs to be addressed.
- The MAPPs pathway provides an ideal opportunity to 're-write the social contract' between regulators, HTAs, payers, clinicians and patients, and this re-drafting will be necessary to make the pathway work on a sustainable basis.
- MAPPs also offers the prospect of economic return in the form of a strong boost to mid-sized biotechs in the UK, in addition to getting drugs to patients more quickly.

Discussions Points at Meeting

Stakeholders: Industry engagement

Industry was described as being keen to engage, but had been rather cautious, perhaps due to the uncertainty in the process. Industry representatives said that ‘everyone’s learning together’ and that this collaborative process was a positive step. The safe-harbour concept has been well received.

For future engagement, it’s essential to understand the economics of the MAPPs model and identify types of targets where the opportunity stacks up financially. This includes reducing the uncertainty around the pricing/reimbursement model. This will help industry, which is currently very risk-averse to be more adventurous with future proposals.

Stakeholders: NHSE engagement

NHSE is still unsure about the merits of a MAPPs approach. The system could be seen as ‘getting the NHS to pay for clinical trials’. The NHS also needs to see a financial model that *stacks up* for the public purse. The uncertainty over the effect of the MAPPs model on pricing is restrictive to all dialogue and discussions.

This latter end of the pathway, particularly introducing new reimbursement schemes, needs addressing with some level of urgency. In particular the following points were identified for further work:

- Understanding HTA perspectives and developing the toolkit to enable their decision making processes;
- Generating the right RWD evidence;
- Developing the UK’s ‘front door’ for such initiatives, including engaging with NHSE and patients.

Resourcing of the programme, for national and international agencies was identified as a major issue that needs to be addressed.

Stakeholders: Patient engagement

Attendees agreed that getting patients involved early is crucial. MAPPs is seen as an opportunity to create endpoints that are meaningful to patients and involve patients earlier in the development cycle. It was suggested that evidence of patient consultation could be an obligatory pre-requisite for entering the MAPPs pathway.

Pricing and reimbursement

Pricing and reimbursement models were noted as the single most pressing issue for the MAPPs pathway. All stakeholders agreed that whereas the regulatory toolkit is available, there is a need for more exploration of incentive structures and more clarity on ‘who pays for what when’, as well as a better understanding of the range of pricing outcomes that would be acceptable to all stakeholders. This issue was clearly concerning to NHSE, patients and industry.

It was also noted that the evidence required to demonstrate a ‘value proposition’ is different to that generally required for regulatory approval, and that having an

understanding of the data required for reimbursement, as part of an evidence package defined earlier in the process, would be essential for earlier dialogue on pricing.

The variability of methods used across HTA bodies in different European countries is also a challenge for defining and developing this aspect of MAPPs.

Real World Data

Overall, participants felt that there was still a great deal of uncertainty over what data and endpoints would be appropriate for inclusion as real world data (RWD), and how to obtain high-quality RWD. There were particular concerns over the typical lack of quality of life data, and the tendency to use endpoints that are easily measurable but may not be sensitive to detecting drug effects and/or relevant to patients.

Natural history of disease data, and a good understanding of disease epidemiology, were noted as particularly important for rare diseases. Here there are often too few patients to have a control arm; this is one situation in which RWD is already used and this should be promoted more widely.

It is also important to collect data on the impact of an intervention on the patient, their carers and the system as well as the purely clinical benefit of the medicine. This will help with cost effectiveness and value analysis.

The Accelerated Access Review should consider options for innovative pricing. There was strong support for additional meetings/subgroup meetings to explore and define options in this area.

New social contract

MAPPs was seen as a way to 'reset the social contract' between regulators, HTAs, the system and patients, both in terms of levels of risk and uncertainty and in terms of the value placed on different outcomes. Flexibility on all sides will be key to achieving this.

It was noted that accepting additional uncertainty in decision-making will inevitably lead to more early approvals that are subsequently withdrawn. Conveying this to the public and the media was thought to be challenging, especially in terms of managing the societal reaction if/when initially promising products are later shown to be less promising than expected.

Next steps

It was agreed that more discussion would be required on several points raised, and that convening the key stakeholders for further meetings would be advantageous. It was suggested that more patient representation, more representation from NHSE and clinicians, and involvement of the devolved administrations would be appropriate; although it was also noted that the group should not be allowed to become too large.

- A subgroup discussing reimbursement models is of high interest, and could report back to the wider group with proposals.
- A subgroup discussing real-world data could also be helpful in addressing some of the practicality issues.



Throughout it was noted that all the agencies and individuals around the table are contributing to the MAPPs pathway without being paid to do so, and that some kind of resourcing specifically for the pathway will be essential to sustain progress.

Contributors to this part of the work

- Megan Morys, CASMI
- Elin Haf Davies, CASMI
- Liz Morrell, CASMI

Chapter 5: Expert opinion - Implementation of real world data collection relating to early access schemes

Background

A key step in the MAPPs process is the collection of RWD and how it can generate meaningful real world evidence (RWE) along the MAPPs decision pathway. From the previous workshops, participants highlighted uncertainty around both the quality of RWD, how it would best be collected, and how it would translate into genuine patient benefit. For all other stakeholders RWD collection in the MAPPs process would be required to help make decisions around safety, efficacy, effectiveness and reimbursement.

Hence we have addressed 3 research questions:

1. What systems, institutions and processes need to be in place to support the collection of RWD in support of early access schemes?
2. Does the system have the right capability, capacity, and culture to support the requirements for early access schemes?
3. What capability/capacity/culture change is required/must occur?

Scope

The scope of this study consisted of a) NHS England b) Examples in pre and post regulatory authorisation space, c) Use of pharmaceutical agents as an example to test other fields (technologies, diagnostics or digital).

Out of scope was a) Justification for having a conditional reimbursement route b) Entry criteria for MAPPs, c) Details of specific RWD to be collected d) Mechanisms for conditional reimbursement including managed entry schemes and price [costings], e) Details of innovative study designs for pre-market authorisation.

For this report Real world data is defined as: ‘Data that are collected outside controlled constraints of conventional randomized control trials to evaluate what is happening in normal clinical practice’¹⁸. This includes, observational studies, audits, registries, eHealth, digital technologies and patient reported outcomes.

Methods

Twenty four semi-structured interviews were conducted from experts within the following sectors: healthcare, academia, pharmaceutical industry, regulatory bodies, governmental institutions and research institutions (Appendix 3, Table 2). Stakeholders were recruited using purposive sampling and snowball sampling techniques.

Each discussion lasted approximately 45 minutes. The interview questions were first developed from a multi-level structural matrix. The first three structural levels were organised at the i) **Individual**, ii) **Systems** and iii) **Organisation** levels. After these three levels were established, the levels were further organised by a) **Capacity**, b) **Capability** and c) **Cultural** factors [adapted from¹⁷] to understand the multi-directional influences of each factor at the three structural levels (Detailed table in Appendix 3).

Three clinical experts with experience of collecting RWD were identified and interviewed from disease areas; cancer, cardiovascular disease and dementia, as an example of the three major archetypes. Seven experts who were involved in the process of RWD management (e.g. bio - and medical informaticians/software engineers, database systems users, big dataset users) were also interviewed. Additionally experts were also recruited from the pharmaceutical industry, regulatory bodies and governmental institutions. Four experts from the pharmaceutical industry, three experts from governmental institutions and two experts from regulatory bodies were identified and interviewed.

Analysis

Expert opinions were transcribed from written notes, analysed together via thematic analysis using the Framework method which identified the themes for each factor at their respective structural organisation levels ¹⁷. Distinctive themes emerged from two sets of experts. Major themes emerged from the clinical and data management experts (from here called healthcare research respondents). Another set of distinctive minor themes also emerged from experts representing the regulatory bodies, governmental organisations and industry (regulator, payer and industry respondents). The two sets of experts were then grouped separately and re-analysed to utilise the full potential of the emerging themes from each group. The results are also organised to discuss the themes between the respective groups.

Results

Real world data and the current landscape – Healthcare research respondents

The healthcare research respondents group consists of the clinical and data management experts (healthcare professionals, academics and bio-informaticians/software engineers). Key themes are summarized in Figure 1.

The Individual Level – Capacity, Capability and Culture

At the individual level, seven themes were identified and organised as follows:

- *Capacity*
 1. Labour intensive
 2. Time intensive
- *Capability*
 1. Input burden can be high
 2. Data input is not uniform
 3. Human expertise is not always available
- *Culture*
 1. Data sharing is problematic
 2. Motivations to collect data is unreliable

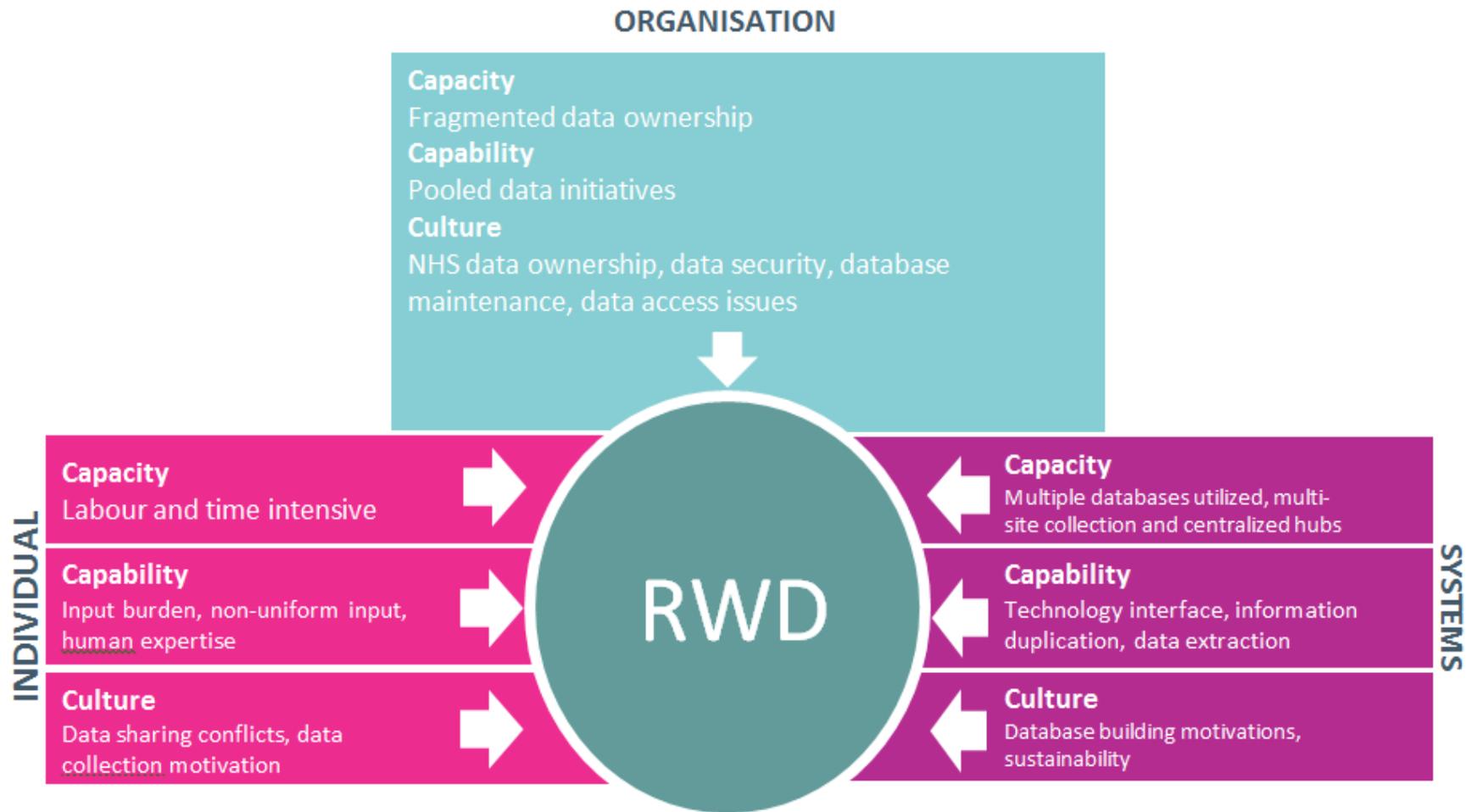


Figure 1 Real World Data - Current Landscape from Healthcare Research Respondents



Healthcare research respondents typically entered data for themselves, particularly data collected for research purposes. In many cases, retrospective data were collated from multiple sources such as patient notes, electronic patient records and imaging. These data were then entered into one database system by clinicians. Data entry of this information was not straightforward due to the inconsistency of adding patient notes to the same source. Depending on preference, notes could be taken only in patient notes and not updated in electronic patient records. Annotations in the database were necessary to cover gaps in information and any questions about information from retrospective data. The administrative process to chase the files, collect the data and obtain full datasets from internal and external sources was time intensive for respondents.

In some cases, healthcare research respondents spent 2-3 hours entering data for one patient dataset. There were subtle variations in the medical codes used by departments or specialists and the clinical context required interpretation by a clinician. Human expertise such as administrative coding assistants and medical coders was not always available to assist healthcare professionals with data entry.

Competition amongst research groups and with other healthcare professionals could potentially induce wariness or reluctance to share data. Research groups that invested their time, effort and funding to collect data for a research project potentially reduced their willingness to share data with other groups. Also, motivations amongst respondents were split between academic funding requirements for clinical research and the demonstration of quality of clinical services. Academic funding requirements included publication pressures and the commitment to publish findings from research projects. Clinical services focused on performance audits and the ability to evidence patient-oriented care.

The Systems Level – Capacity, Capability and Culture

At the systems level, eight themes were identified as follows:

- *Capacity*
 1. Multiple databases may need to be utilized
 2. Multi-site data collection via centralized hubs may be necessary
 3. Cost considerations for real world data
- *Capability*
 1. Technology interface issues exist
 2. Duplication of information can occur
 3. Data extraction is challenging
- *Culture*
 1. Database building motivation may be inconsistent
 2. Sustainability is not assured

Healthcare research respondents collected data for multiple purposes in multiple systems. Data collection was dependent on the purpose and how respondents' time was split amongst clinical activities and research activities. Multiple systems could be used:



NHS databases, registries, ad-hoc or bespoke systems, and laboratory data. A large number of respondents participated in multi-site data collection via centralised hubs. This process gave equal access to data and the ability to live feed data from a subsystem to a central system. Some respondents preferred to use an available dataset gathered from data providers who give access to real world datasets from clinical practice and hospital trusts. The cost and time considerations were drastically reduced in comparison to collecting new data.

Health research respondents largely worked in systems that did not interface with each other. These systems, without an integrated function, required duplication of patient information and data entry to each source. Due to the multiple systems and datasets, data extraction became a challenge. Respondents felt the process was inefficient and difficult to extract data from systems or to integrate data to systems.

Currently, database building motivations may be inconsistent. For many respondents, data were collected for local purposes. Each new database was built for purpose to suit a new project and varied in its origin and cost. Software and operating systems may originate from different manufacturers or the infrastructure outsourced and built by an external party. Respondents approached multiple suppliers to consider cost and user interface of each system to identify a suitable system.

Moreover, datasets that were provided by data providers were separated into multiple files. The files then required integration and cleaning. Ad-hoc databases were built to accommodate for this recurring feature from data providers. This process also required respondents to modify timelines to accommodate for the extra time and labour involved in maintaining the datasets.

However, using a bespoke or ad-hoc system for each new project does not necessarily indicate long-term sustainability of a database system. Attempts were made by a small number of respondents to re-purpose datasets, but issues arose with compatibility of datasets, consistency in the collected data and funding to ensure longer-term research purposes. Currently, funding for research projects can only cover up to 5 years at a time which may be difficult for larger population studies or big datasets.

The Organisation Level – Capacity, Capability and Culture

At the organization level, six themes were identified as follows:

- *Capacity*
 1. Data ownership is often fragmented
- *Capability*
 1. Databases need to be pooled
- *Culture*
 1. NHS data ownership is unclear
 2. Data security needs to be assured
 3. Database maintenance is a long-term need
 4. Data access needs to be carefully managed



Many healthcare research respondents reported that data ownership was also dependent on the type of project and the type of data that was involved. For most respondents, data were stored on an NHS server on a trust level and a national level. For other research, data could be owned by a university but housed on an NHS server. Research institutes also housed and allowed access to clinical datasets for research purposes.

Database systems need to be pooled to link up systems for access to datasets. Integration of databases was seen within trusts or on a national level in the NHS, but national to trust level linkages were challenging to achieve. Practical issues also arose when live feeding data into one system due to the lack of harmonization of medical technology among healthcare departments and specialists.

The question of data ownership was met by two types of opinions amongst respondents. Many respondents preferred the NHS to store and house patient data. A small number of respondents had no real preference. Third party data providers or data stewards could also house data for the NHS provided that security measures were followed to a high standard. Data encryption and a secure firewall were of the highest priority to respondents. Furthermore, patient anonymity, confidentiality and consent should also be at the forefront of security measures to protect patient information.

Healthcare research respondents noted that database maintenance was a long-term need. Funding support is required to actively maintain a database system and services; however steps should also be considered to reflect sustainability to maintain databases on a longer-term basis, particularly if data is re-purposed or integrated to other datasets.

Some healthcare respondents encountered challenges in accessing datasets. While multiple data providers house data and provide data access, bureaucratic issues (e.g. duplicating applications to multiple providers for similar NHS datasets) caused delays to project timelines.

Real world data and the current landscape – Regulators, payers and industry respondents

Themes from regulators, payers and industry respondents were distinctive from their healthcare research counterparts:

1. RCT data (efficacy) versus RWD data (effectiveness)
2. Standard minimum set of outcomes for disease area
3. Question of responsibility, ownership and cost of RWD collection and post-RWD collection
4. Data access and confidentiality



Many of the regulator, payer and industry respondents focused on the difference between efficacy and effectiveness in data collection. RCT data could provide insight to the intended effect of a drug treatment under ideal circumstances. RWD can provide insight to the degree of beneficial effect in real world settings through clinical practice. RWD are prone to biases and confounding factors, but give different information from RCTs.

A small number of respondents suggested that RWD could complement RCT data in a progressive process to measure efficacy and then effectiveness.

Regulator, payer and industry respondents considered data standardization on a broader level by establishing a minimum set of outcomes by disease area. In previous cases, drug-specific registries were created and had less potential to be maintained for other uses. However, there is a lack of agreement to finalise the framework that would determine the minimum set of outcomes and on what scale the implementation would occur (e.g. local, regional, national).

The question of responsibility, ownership and cost to collect RWD and post-RWD collection was one of the major concerns amongst regulator, payer and industry respondents. Industry sponsors may cover the cost of data collection until marketing authorisation, but after this period, the responsibility to collect RWD is unclear. It may also be difficult for SMEs to cover the costs of both additional administrative costs early in the pathway, and subsequent costs of RWD collection. The costs could present an arduous challenge for small companies, if re-imburement was unavailable between stages. After RWD is collected, the question of responsibility and costs to maintain and house the data is particularly unclear.

Data access within and across studies and confidentiality were also concerns of regulator, payer and industry respondents. Collaborative constituencies occur between industry and the NHS to collect patient data; however confidentiality and levels of access come into question. Access levels may be required that limit the visibility of patient information to the necessary staff members, particularly if external staff members are involved in the process.

Case Studies

Highlighted briefly are 3 case studies of ongoing RWD initiatives in the UK that could be used for framework for the development for MAPPs process of RWD collection and utility.

Systemic Anti-Cancer Therapy (SACT) Dataset

The SACT database is a repository commissioned by the National Cancer Intelligence Network (NCIN) for data on all cancer treatments in all treatment settings in England. Submission of data to SACT began in 2012 and have been mandated since May 2014. It receives datasets from a total of 170,000 patients across 144 trusts. SACT benefits from national support bodies, existing infrastructure, electronic prescribing systems and its data is unbiased. Despite its framework having the potential to be highly applicable for



linkage to other datasets and other diseases, concerns were raised from respondents highlighting continuing interoperability challenges between local data extraction and a national repository database (SACT).

100,000 Genomes database

This database is a Genomics England medicine initiative to sequence 100,000 genomes from 70,000 NHS patients by 2017 with rare diseases or common cancers

Currently there are eleven genomic medicine centres across the nation in linked systems to have equitable access to data. The first diagnostic success of this project has recently been reported (<https://www.geneticliteracyproject.org/2016/01/13/first-diagnoses-signal-success-100000-genomes-project/>), however it is still early stages and for cancer data entry is currently retrospective and manual.

Salford Lung Study

The Salford lung study is collaboration between: GlaxoSmithKline (GSK), North West eHealth (NWeHealth), University of Manchester, Salford Royal NHS trust foundation, NHS Salford, 80 GP sites and community pharmacists. It was labelled a global first 'real world RCT' (pre- MA medicine vs standard of care) for evaluating safety and effectiveness of a new treatment for patients with asthma and Chronic Obstructive Pulmonary Disease (COPD)

It is an open label study with, broad inclusion criteria, using the minimal required outcomes data from RCTs (Quality of Life QoL, EQ5D, Adverse Events AE and GP visits). It utilizes a Salford developed (NWeH) 'shared care' records for integrated primary and secondary care. For example, the NWeH system will notify the study safety team if a patient in the study has had an adverse event. The appropriate action can then be taken. While this study's ongoing success could prove a pivotal test case for future RW RCTs it is yet unclear if its local framework could be applicable nation-wide.

In addition to the above, a few other local RWD initiatives are highlighted here: i) Birmingham NHS trust Prescribing Information and Communications Systems (PICS) - a decision support tool incorporating medicine prescribing and administrative data, ii) Health e-data (HED) - linking HES and death data across England, iii) General practice research database (GPRD) is one of the biggest computerised database of longitudinal anonymised primary care data¹⁸.

At the heart of the Clinical Research Network's activities is the NIHR Clinical Research Network (NIHR CRN) Portfolio. This consists of a large number of high-quality clinical research studies that are eligible for consideration for support from the Clinical Research Network in England

There is also an emergence of crowd sourcing of data from websites such as 'patientslikeme.com' - using patient reported data related to medications, symptoms, and experiences which offer potentially meaningful data resources for decision processes on effectiveness and safety in the real world.



Current positives for ongoing RWD initiatives:

- Large number of **local RWD** initiatives and collaborations cross cutting data variables, disease, geography, unmet clinical needs
- Increasing number of **nation-wide** 'hubs' and 'communities' of RWD excellence for eHealth, Big data, disease and geography specific entities involving multi-site, multi-stakeholder and EU partners (Salford lung study, SACT database, 100,000 genome)
- **Expanding base of IT**, data analytics, bioinformatics and machine learning experts within and across NHS trusts and university collaborations
- **Forward thinking** champions such as; eHealth-NWeHealth, digital health -FARR institute
- Growing **patient engagement** and acceptance of clinical research data sharing and patient use of mHealth such as 'Citizen Scientist' (www.citizenscientist.org.uk)

Real world data and improvements to the current system

Recommended improvements to the current system were consistent amongst all of the respondents. The structural organisational levels as organised by capacity, capability and cultural factors visually capture the recommended improvements by respondents (**Error! Reference source not found.**).

The Individual Level – Capacity, Capability and Culture

- *Capacity*
 1. Increased IT Support
 2. Better quality data
 3. Database integration
- *Capability*
 1. Better user interface
 2. Increased systems functionality
 3. Prospective data collection
 4. Coding standardisation/uniformity
- *Culture*
 1. Controlled data access permissions

Respondents recommended increased IT support with regard to both staffing and funding. There is often funding to create databases during the duration of a project, however, there is not often funding to maintain the database after a project is completed. IT support could also include database integration and mapping of codes and data items.

Better quality data in datasets could be achieved through two principle factors: prospective data collection and coding standardisation/uniformity. Prospective data collection would allow for real-time data entry that would save time and labour and



would not require interpretation by a third party. Queries about entered data could be asked directly to the healthcare professional providing it. Data quality could be enhanced by harmonising medical codes and standardising the data entry procedure.

User interface is also an important factor to consider to increase systems functionality. Enabling a respondent to enter data to a database that is user-friendly and straightforward enables the process to be time-efficient. Systems functionality could be improved by regularly updating the required data items in the database to reflect medium-term changes to the system.

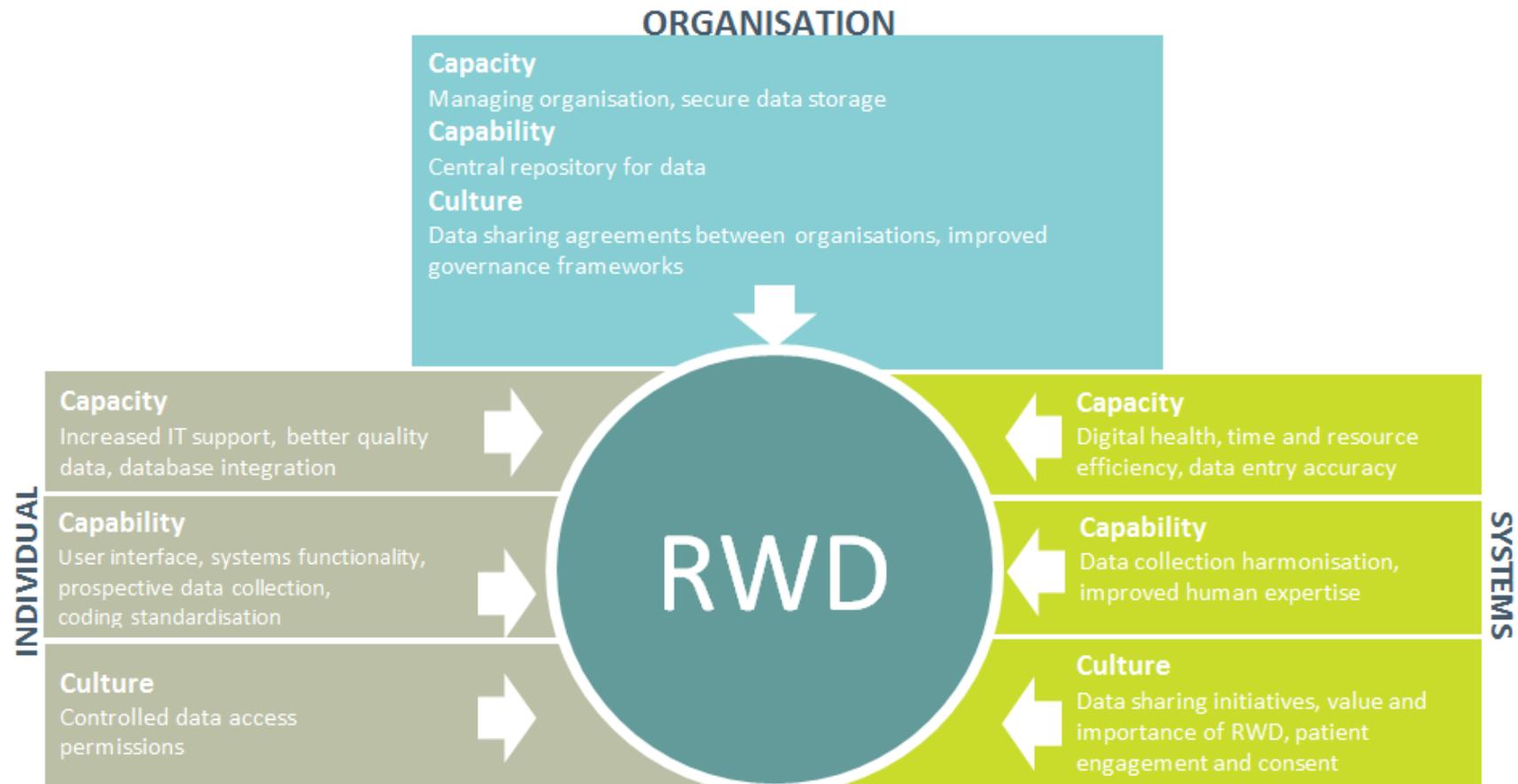


Figure 2 Improvements to the Current System

The Systems Level – Capacity, Capability and Culture

- *Capacity*
 1. Digital health
 2. Time and resource efficiency
 3. Data entry accuracy
- *Capability*
 1. Data collection harmonisation
 2. Improved human expertise
- *Culture*
 1. Data sharing initiatives
 2. Value and importance of RWD
 3. Patient engagement and consent

Respondents were interested in pursuing digital health options and patient provided/driven data. With patient data, suggestions such as patients filling out their own information in questionnaires or having their data sent automatically from devices to a central database system. Incorporation of digital health and patient involvement would be time and resource efficient and increase data accuracy.

Improved data collection harmonisation was related to the standard set of outcomes mentioned by the regulator, payers and industry respondents. Data collection could be set at a national level with a minimum set of indicators, but the database system could be modified for local purposes. The database would require flexibility in order to fulfil national and local objectives. In order to achieve requirements on both the national and local levels, human expertise would be required to progress the IT development during the entirety of the database systems and infrastructure building process.

Data sharing or data collaboration initiatives could improve the state of wariness that is experienced in the current landscape. Some respondents mentioned forums amongst research groups such as the Big Health Data User Group or the Health Information Network. Respondents suggested that transparency in research and awareness of data that is utilised amongst researchers could decrease the tendency to have research silos.

Whilst RCT data is the gold standard currently, there must be recognition and awareness of the value of RWD. Respondents distinguished between the two types of datasets and research designs, stating that they both have their own strengths and limitations. RWD has the potential to provide insight to long-term outcomes and follow-up information that RCT data cannot provide. For population studies, RWD is an important and valuable resource that is available to access.

Respondents also pointed out that patient engagement and consent process should be sought when using data for future use. Providing feedback to patients at each step of the process was one method respondents thought patient involvement could be maintained.

The Organisation Level – Capacity, Capability, Culture

- *Capacity*
 1. Single managing organisation
 2. Secure data storage
- *Capability*
 1. Central repository for data
- *Culture*
 1. Data sharing agreements between organisations
 2. Improved governance frameworks

Respondents suggested two types of improvement for data storage and responsibility. The first was to have one managing organisation as the data provider for NHS datasets or to have a hub to that would act as the gateway or ark to apply for data access through one channel of information governance. The other option was to have a central server or central repository that provided linked datasets that could be accessed by multiple data providers and send out integrated files of data to recipients.

Current barriers to successful RWD collection:

In summary, some of the key barriers to RWD collection are as follows:

- **Importance** and **effectiveness** of RWD unrealised by industry/NHS/healthcare/regulators and patients
- **Incentives** for RWD collection at all levels lacking
- **Data linkages** challenging both intra and inter NHS Trust
- Ethical and legal **frameworks** for data too complex and rigid to accommodate disease, geography and local Trust variances
- **Data access and security concerns**
 - who owns what and when, and who accesses it?
- **Time** and **resource** limitations for data collection

Learning from Commissioning Through Evaluation

NHS England has invited providers to apply to take part in a new Commissioning through Evaluation (CtE) programme which enables patients to access promising new treatments which are not routinely commissioned, whilst new data is collected within a formal evaluation programme. While there have been a number of recent announcements in the UK for procedures under such a scheme including; Stereotactic ablative radiotherapy (SABR) and Selective dorsal route Rhizotomy (SDR), it is still too early to assess the successes and pitfalls.

Several larger studies in Denmark however have assessed the utility of RWD collected via observational data and patient registries for therapies where early access or CtE were warranted. In one case of Oxaliplatin (treatment for colon cancer), simulated follow-up data to the empirical data available through the

registry was analysed for applied value of information against the costs of registering patients over a 4 year period. A second study compared prognosis, treatment and effectiveness outcomes in clinical trial data compared to daily practice data for Bortezomib (multiple melanoma). In both cases it was concluded that the quality or quantity of the RWD was either ineffective¹⁹ to make a meaningful reimbursement decision or insufficient to make a decision on safety or effectiveness²⁰. Policy and decision makers should be aware of the limitations of current RWD collection and carefully consider the types of RWD required for a decision mechanism.

RWD governance

Good data governance practice is a vast and ever changing arena covering a number of key principles that are highlighted in the below table. All countries have similar practices per se regarding how data should be handled, national policies for the collection and use of care data differ between countries, and the legal framework often not entirely prescriptive. While a detailed evaluation of data governance is reported elsewhere²¹, the best examples are those that follow a clear and transparent recognition of ethical and legal concerns around patient anonymity in parallel with an appreciation of the value of public research. In general, data collection and access for service evaluation and audit don't require patient consent, while data processing for research processes generally does require consent (with country specific provisions for exemptions – i.e. UK section 251). This in turn leads to a differential framework for data providers and access, some of which are highlighted here.

For patient level data, providers and access are available as follows:

- **Routinely collected patient data**
 1. Health and Social Care Information Centre (HSCIC) who govern and provide information and data
- **Information providers**
 1. HSCIC holds Hospital Episodes Statistics (HES) – A&E, outpatient, NHS hospitals
 2. Clinical Practise Research Datalink (CPRD) is the English observational and interventional service
 3. MHRA+NIHR provide primary data from GPs (anonymised by HSCIC before getting to CPRD)
 4. IMS health- collect data on pharmaceuticals at primary care levels and secondary (patient) level through Hospital Pharmacy audit (HPA)
- **Data access**
 1. NHS and commissioners apply via the Secondary Uses Service (SUS) and non- commissioners apply via the Data access Advisory Group (DAAG)

Data usage for research purposes require national (NHS R&D or social care research) and local (trust and research centre) ethical approvals (REB).

All types of interview respondents expressed concerns that the current UK framework was too complex and rigid to both maintain data protection and patient confidentiality and support collaborative efforts for RWD collection.

With the boundaries of clinical and research data blurring rapidly in a drive to permit early access and novel reimbursement pathways, combined with new UK and European data protection legislation coming into effect by 2018, an appropriate ethical and legal framework that is agile, resilient and responsive to local and national needs, supportive of public and privacy interests of health care data, and meets the regulator and HTA needs is imperative. Aspirational frameworks have been proposed and will be closely scrutinised following new EU legislation ²¹.

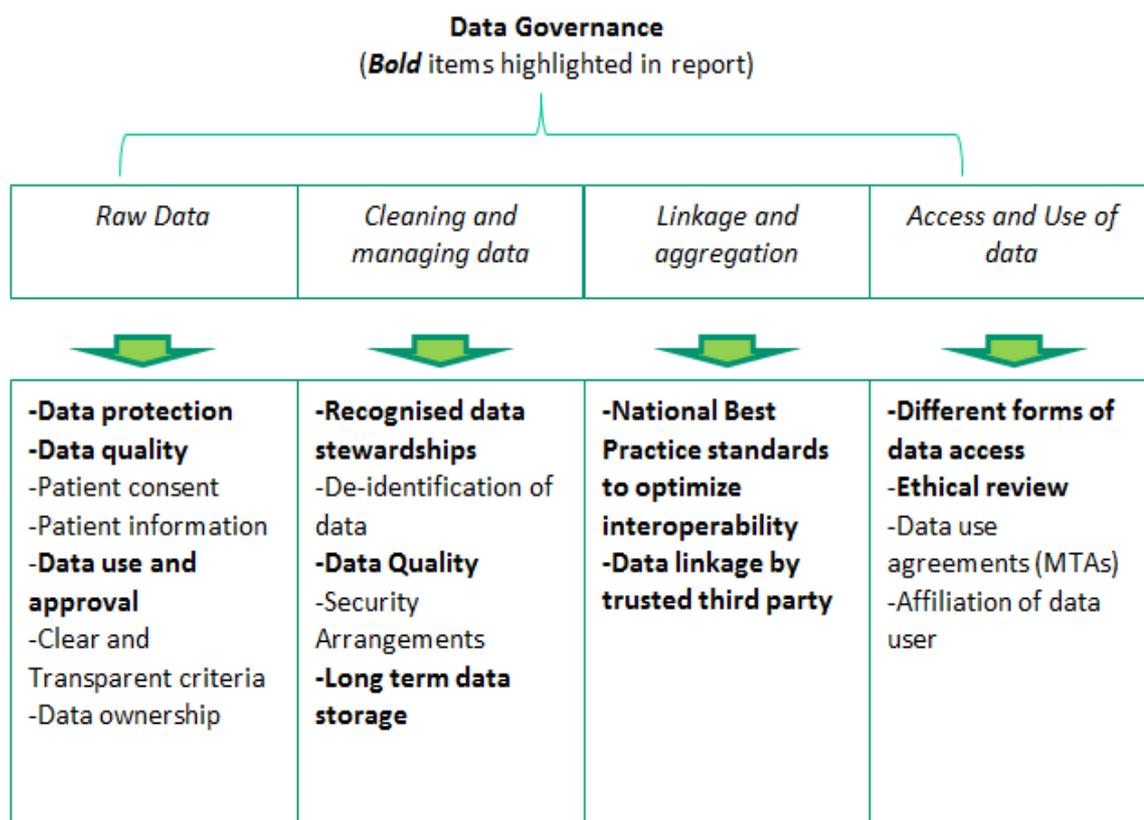


Table 1 Data Governance framework - Adapted from ²¹

Flexible approaches for RWD collection

With the rapid development of digital health- the patient being the driver and inputter of health data, and the resulting dearth of data generated poses a number of issues around the type and structure of RWD generated compared to that of a traditional RCT. The below thought experiment comparing a generic oncology drug to a wearable device (i.e. Jawbone bracelet) highlight some of those considerations requiring a dynamic and flexible approach across different RWD types for collection, analysis, comparators, storage and ownership.

Variable	Oncology Drug	Digital Technology (Wearable devices, Apps, etc)
Outcome measures	Small number of outcome measures: i.e. Progression free survival, overall survival	Large number of outcome measures: i.e. Activity levels, Sleep levels, Physiological (MABP, HR, temp, blood glucose), Patient Reported Outcomes (pain, psychosocial, diet)
Adverse Events	Benefit/risks defined	Benefit/risks variable and poorly defined
Surrogate marker	In some cases known: i.e. response rate or tumour shrinkage, Health-related quality of life using a standard tool	Largely unknown
Outcomes validated	Largely validated against clinical standards, Patient characteristics, and resource use to calculate costs.	Largely not yet validated against clinical standards (i.e sleep quality App vs Pittsburg Quality Sleep Index)
Data collection	Minimal required data at defined time intervals (i.e. BL, 6 and 12 months)	Data collected continually
Data structure	Largely known and discrete	Highly variable per outcome and per device
Data Ownership	Industry/NHS/Third party known	Undefined or variable (patient, technology company industry, pharma, NHS)

Table 2 Examples of differences in data requirements, type, quality and quantity between medical technologies

There are a number of large country wide initiatives across data sources, disease states and technologies working as hubs of excellence for RWD collection, data stewardship, analysis and interconnectedness. These could be better utilized and expanded to encompass both additional disease states, collection sites, data platforms and health cities (those city regions with large enough populations to offer scientific influence yet small enough to ensure engagement with communities over health data use and be attractive to both small and large businesses as a test bed for innovative products).

Recommendations and next steps

- Champion the **importance and value of RWD** at all levels (patient, healthcare provider, regulator, payer, industry)
- Develop clear **best practise guidelines** for all stakeholders for minimal RWD needed to generate meaningful RWE for safety, effectiveness and reimbursement decisions.
- **Engage** patients early in **transparent consent process** including the 'future use of data', flagging eligibility, and patients being the 'drivers' of data input

The above will in turn support the development of:

- More **flexible** data and ethical governance **frameworks** to support local and national RWD collection
- **Standardization and harmonisation of data collection:** agreed working frameworks, universal codes, harmonised interfaces

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Chapter 6: Challenges to implementation of MAPPs in the UK

Uncertainty about the reimbursement aspect of the MAPPs process is causing concern amongst all stakeholder groups involved in this initiative. Urgent work is needed to address how such an approach in practice could work, and to reassure all parties that such an approach can be sustained in the current health care system. Lessons learnt from the high pricing of Orphan Drugs can be applied to ensure that such issues do not compromise the success of a MAPPs approach.

Drug development is a global exercise. As such, the value of initiatives that impact on the drug development process are considered in terms of global commercial value, and not just in one country or region. The cautious response by industry to EAMS, compared to the EMA pilot scheme is likely to be a reflection of this.

Integral to the MAPPs approach is the marriage of clinical care and research in generating real world evidence through RWD collection. With an earlier decision process for safety, efficacy and reimbursement, best practice agreement of the quality and quantity of data collected outside (and in parallel) of the gold standard RCT is vital. This can in part be facilitated via a realization of the value of RWD by all stakeholders. The UK has a vast array of databases and growing number of RWD initiatives whose expertise and infrastructure should be utilized. Similarly, the scientific approach implemented in a clinical development plan must be one that can be adopted across many jurisdictions when patient recruitment requires multi-national sites with differing ethical, legal and governance frameworks

To be at the forefront of MAPPs development the UK must be able to demonstrate how our initiatives and approaches are complementary to, or easily translatable to other countries.

Finally and fundamentally, for a MAPPs approach to be successful in today's society, it will need the complete *buy-in* from patients and their carers. While early signs indicate that patients are receptive to this (see Chapter 2), on-going and continuous communication is essential, involving the patients in the design of an approach before initiation. Such an approach would be mandatory to encourage patients to participate in clinical research, empower patient decision making on risk/benefit and manage trust and transparency issues that might emerge, especially when drugs are withdrawn (either for safety or efficacy reasons) as new evidence emerges.

Overall next steps to support the implementation of MAPPs

Some of the issues raised in this report that need to be addressed imminently to support MAPPs implementation are as follows:

- **Address the pricing and reimbursement issues across all stakeholders**
This would be addressed through the ongoing AAR.

- **Ensure adequate resourcing among agencies**
Additional resources are required for the implementation and uptake of these new adaptive pathways and could be supported through the AAR.
- **Include clinicians in future cross-stakeholder discussions, to identify the impact of MAPPs on clinical practice and any barriers that would arise.**
This warrants immediate exploration of barriers and subsequent enablers.
- **Facilitate mechanisms for engaging patients and advocacy groups in the entire MAPPs process**
Open and continuous communication through advocacy groups and engagement forums like ‘citizen scientist’ to ensure that patients are included in all stages of the pathway including risk/benefit decisions for treatment.
- **Place the UK at the forefront of EU initiatives that encourages early access of products**
Ethical concerns raised here and by all stakeholders must be identified and addressed as they arise with strong links to and learnings from other similar schemes in the EU.
- **Develop a working landscape of current UK RWD initiatives (eHealth, Big data, analytics and digital health).**
A working geographical and expertise map of UK RWD initiatives would enable swift assessment of barriers and bridges to MAPPs as they evolve. This would parallel with the current EU initiatives under IMI –i.e. GetReal and ADAPTSMART projects.
- **Champion the importance and RWD across all stakeholders**
A cultural shift will foster open collaboration and the development of tangible best practice guidelines.
- **Utilize existing UK forums as mechanisms for cultural change and engagement** across all stakeholders (i.e. Academy of Medical Sciences, and Association of the British Pharmaceutical Industry, held a joint workshop on ‘Real world evidence’, Sept 2015, FARR institute- ABPI Industry Forums 2014, 2015).

Overall Conclusions and Recommendations

MAPPs offers an opportunity to reconstruct the drug development pathway in a way that allows early engagement and shared decision making by all stakeholders, especially patients.

There is generally strong support for the concept of MAPPs from the patients that participated in project workshops. MAPPs success requires meaningful engagement and involvement in the complete process, especially in relation to study design (including justification for placebo arm) and the choice of outcomes selected (relevance to the patients themselves).

Further work is needed to explore the ethical implications of MAPPs, building on the findings of this report. This work may best be done in the context of specific medical technologies (drugs, medical technology, devices), as concerns, uncertainty and solutions will vary.

Similarly with earlier decisions requiring data of as yet greater volume, a rapid review and agreement between stakeholders of IP generation, data sharing and

data protection expectations. It is also essential to engage all other stakeholders further in dialogue to make sure patient expectations can be met throughout.

Pricing and reimbursement is a particular priority. Further exploration of incentive structures, the range of pricing outcomes and demonstrating value proposition, that would be acceptable to all stakeholders is imperative. The use of robust and meaningful RWD as one of the tools during the reimbursement process is highlighted here. However, the issue of reimbursement was clearly concerning to NHSE, patients and industry.

The UK has demonstrated an eagerness to be involved in early access approaches, across all stakeholder groups, from political support to EAMS, to the willingness of both the MHRA and NICE to be part of the EMA pilot scheme. This momentum should be capitalized upon now, but will inevitably require the necessary resources and support.

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Appendices

Appendix 1

Attendees of the ethics workshop:

Category	Title	FIRST Name	Surname	Post	Institution
CASMI	Dr	Sarah	Garner	Associate Director for R&D	NICE
	Dr	Sian	Rees	Director	Health Experiences Institute, Oxford
		Rosie	Pigott	Project Manager	CASMI
		Megan	Morys	Deputy Director	CASMI
	Prof	Richard	Barker	Director	CASMI
Ethics	Dr	Mark	Sheehan	BRC Ethics Fellow	Ethox
	Prof	Michael	Parker	Director	Ethox
	Dr	Ariella	Binik	Postdoctoral Ethics Fellow	Ethox
	Dr	Sarah	Edwards	Senior Lecturer, Research Ethics and Governance	UCL
	Dr	Annette	Rid	Senior Lecturer, Bioethics and Society	KCL
Regulation	Sir	Alasdair	Breckenridge	Chair	ESBAC
		David	Silverman	Medical Assessor	MHRA
Law	Prof	Jonathan	Montgomery	Professor of Healthcare Law, UCL and Chair of the Health Research Authority	
		Paul	Ranson	Partner	Pinsent Masons
	Dr	Peter	Feldschreiber	Barrister and Physician	4 New Square

Industry	Dr	Nick	Edwards	Chairman	MedInnovate and Kinapse
	Dr	Geoffrey	Guy	Chairman	GW Pharma
Clinical	Prof	Houman	Ashrafian	Associate Professor of Medicine, Head of Experimental Therapeutics	Oxford University
Personalised Medicine	Dr	Ingrid	Slade	Director	Centre for Personalised Medicine
Patients and public		Helen	Haggart	Head of Policy	AMRC
		Mark	Stone	Trustee	MND Society
		Carer for Mark Stone			
		Alan	Chant	Patient Representative	Multiple Myeloma
		Daniel	Bridge	Policy Manager	CRUK
		Emily	Crossley	Trustee	Duchenne Children's Trust

Appendix 2

This appendix includes unedited comments from the patient workshops, to provide a direct flavour of the discussions:

Emerging themes placed under the Personal Perspective

Emotions

- Major fear of delays, especially for progressive diseases such as these experienced by participants in the workshops
- Need for support or coaching /counseling for decision-making (emotional support)
 - However noted that this is time consuming and costly
- Making treatment decisions is an emotional burden
 - But the alternative is that you/your child is going to die
- It's painful to watch your child deteriorate when they know there's something out there that could help
- Emotional support from patient groups considered by many to be essential and invaluable
- Heartbreaking when patients are excluded from a trial due to narrow inclusion criteria
- One Alzheimer's patient expressed great fear of enrolling on a trial

Attitudes

- Power imbalance between clinicians and patients – with some lack of faith/ trust in clinicians
- Reliance on clinician being up-to-date
- Fear of medication and polypharmacy – from side effect to reliance
- A need for non-pharmacological options and support
- Skepticism towards the pharma industry that only see drug development as a profit making commercial business
- Pharma approach to litigation not helpful; not there for patient benefit just for pharma benefit
- General view of medication for Parkinson's is fairly dismal but accepting, in that medications area considered a necessary evil especially when it's not very effective and can have substantial side effects.

Patient empowerment

- Sense that being involved in process empowers patients to make decisions that are right for them
- Emphasis on moving patients from 'passive patient' to 'patient leadership'

Transparency

- Lessons learned from the thalidomide incident were discussed in two workshops, and the greater need for transparency and regulation since then acknowledged
- The necessary level of trust for a MAPPs approach to succeed can only be obtained from transparency
- Acknowledgement that there may be conflicts for some people – but this must be shared as common knowledge

Communication

- Importance of 2-way communication stressed, so that early indications that there may be a problem are communicated to everyone taking the drug. Regular, general updates could be shared as well.
- Getting the information is more important than how it is communicated; people may want different methods such as letters/websites etc.
- Merit of patients meeting discussed, but benefits and risks from this are possible (e.g. individuals might look for side effects if expected).
- Results of MAPPs process for individual drugs should be published in open access journals. It is empowering for patients to be able to read about the process and what has happened with other MAPPs drugs.
- Information needs to be simple to understand, acknowledging that people forget information and that there is a lot of it to absorb.
- Important to improve the way that patients can find out about trials, and how they can ask to be involved in a trial that's not running in a local center.
- Communicating possible vs actual risk is difficult to get right.
- Complete picture of the MAPPs process is required, including information about drug formulation, as well as information about monitoring, including frequency and level of invasiveness of tests, which would form part of the consent and decision making process.
- Presentation of the risk and the reward needed. Important to include information on how to report / manage adverse events – what to look out for? This information is important for carers as well, and should also form part of the consent and decision making process.
- Reward patients with a certain level of respect in the way and frequency that you communicate with them
- Level of data to share can be a difficult balance between wanting to know all the information, even the minor, to finding too much information a frightening overload.
- Communication to the public should be proactive – not reactive. Efforts should be made to inform the media and the public of future plans and the reasons for it.

Emerging themes under Pre MAPPs

Decision Making

- Patients make decisions based on self-interest but also altruism
 - E.g., benefitting their children/next generation
- Many patients will trust their clinician to help them make a decision
 - This may have positive and negative impact re informed decision
- Tension between side effects and benefits is a problem with taking any drugs
- Patients are capable of choosing
- However other patients may not be as well informed as the participants of these workshops, which would require a certain degree of informing, educating and empowering to make decisions right for them.
- As part of the decision making process it would be reassuring that there still be some regulation to protect patients from 'rash' decisions

Capacity

- What happens when the patient can't consent was a major concern for the participants – particularly when it came to leaving the decision to their loved ones / next of kin.
 - Should someone with power of attorney be able to consent for them?
 - Would a living will apply?

Consent

- Strong feeling that the individual should be allowed to make the choice;
 - Flexibility
 - Consideration of individual context
- Want all information available
 - Must be fully informed about **whole** process: what is not known is uncertain or might be predicted.
- Depends on how ill you are as to whether you can make the decision
- Need for a '*contract*' with the patient.
- Acknowledge that patients may change their mind over time – so consent may need to change.
- Include discussions about power of attorney and living wills, families may be able to continue consent if capacity is lost, but only if discussion is had early, especially as attitudes differ within families.
- State what will happen if the drug 'fails.'
- How would any litigation risk be managed? General agreement that this needs to be included in consent process.

Benefits

- Makes drugs accessible/available more quickly

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- Needs to be a careful balance between safety and speed.
 - How much difference in time is it going to make?
 - Life expectancy and quality of life (incl. QOL for carers)
 - Altruistic desire to help next generation

Risk

- Every individual's perception of risk is different
 - Cannot be one size fits all
- Disease severity impacts acceptable level of risk
- Level of benefit
 - E.g., quality of life valued versus quantity: curative very positive
- Risk of destabilising one's condition is a real worry
- A lack of understanding of whether the risk was related to a risk of harm or a risk of the drug not working was identified as a major source of confusion. This has significant impact on the level and type of communication to illustrate these risks in a suitable way for patient comprehension
- Complete transparency is needed in what patients need to know in the consent process

Emerging themes under a MAPPs Process

Study Design

- Having a placebo arm was considered unethical, especially in life-limiting diseases by participants in two of the workshops
- But the need to ensure that the evidence generated is still robust was also acknowledged
 - What are the alternatives to RCTs that could be considered acceptable to all without lose scientific rigor?
- Making the process quicker was a big appeal.
- Use of digital technology is enabling and should be encouraged more
- More feedback throughout the process, and much earlier insight into results sought
- Part of the design is the contract with the patients including legal issues and involvement of patient in design
- Concern as to whether it will take longer with real world data to get the answer, as not knowing whether if the drug works is a problem
- EU approach/collaboration could increase numbers of patients available and collaboration between different stakeholders

Eligibility

- Hope that MAPPs would broaden the cohort eligible for inclusion in future studies

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- MAPPs considered most suitable for when there isn't already an effective treatment, not just for incremental benefit – probably not the right model.
 - Significant benefit / no effective treatment. Suitable for groups of patients whereby they will take on a much greater level of risk because they're faced with imminent mortality. For people like that; MAPPs scheme is really fundamental.
 - People that don't have the time (e.g. life-limiting) to wait for the whole of this process to go through are prepared to take the opportunity of MAPPs because it's the best opportunity that's there
 - Eligibility of MAPPs was considered to apply to virtually any of the conditions which have a chronic long-term impact, and especially those addressing the needs of terminal illness
 - A self-selecting group of volunteers should be considered eligible

Service delivery and prescribing

- There is currently varied provision across the country in terms of care and access to research
- GPs should not be prescribing/deciding on the drug; it should be a specialist
- Some ongoing testing could be done by the GP but they need support from a specialist team
- People were concerned about equality of access if only some consultants could prescribe, and advocated advertising of studies so that people could be aware of them

Monitoring and Data

- Rapid continuous feedback of discoveries from patients themselves and others throughout the process would be required
 - Frequent, rapid feedback
 - The positive and negative effects
- Would expect more frequent contact/monitoring because it's an experimental process
- Carers need to know what to look out for
- Tests may be burdensome: need to consider the implication of this (practical and emotional)
- Risk may be minimised if active surveillance were made available
- Considerable agreement that, if a license is given early, then monitoring needs to be more intense to enable early identification of any potential problems.
- Similarly, the greater uncertainty associated with taking a MAPPs drug might be offset by very active monitoring.
- Assessment of monitoring data should be independent of the drug company.

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- Debate about whether patients should have to commit to monitoring in order to go onto a MAPPs drug, acknowledged that collecting all information is important, but enforcing monitoring may not be possible or desirable.
 - Monitoring might be improved by being real-time, using technology, recording all potential symptoms/side effects e.g. daily patient diaries.
 - How to disentangle side-effects of MAPPs drug in poly-pharmacy? Herbs and natural products may be taken, often seen as different from prescribed drugs, but may also have an impact, therefore need to record if taken.

How to record data

- Digital health technology would allow for more intensive monitoring in a simple and non-burdensome way
- Some people aren't techno-savvy and this needs to be considered in their implementation
- More constant monitoring needed
 - More frequently than just once every 3 months
 - More intense in terms of quality and relevance
 - Might be feasible with digital technology
- Data collection must be simple: tension with comprehensiveness
- Less bureaucratic approaches are needed

What data to record / monitor

- Holistic approach needed in the real world collected – to include data sets linked to quality of life / impact on daily living
- Selection of outcome measures need greater thought
 - Regulatory authorities need to approve but design and selection should be with patient involvement
 - Patients know best what is important to them
- Uncertainty on the choice of appropriate outcomes a major concern for patients

Data Ownership and Sharing

- Differences:
 - Patients want it to be shared and owned collectively
 - Patients with life-limiting want it to be shared widely and anonymised
 - Alzheimer's/Parkinson's patients who participated in the workshops had some concerns over anonymisation and where the data should go, that were generally more cautious than those expressed in the other workshops
- General agreement by everyone that data should be collected
 - Except some people in Alzheimer's/Parkinson's group

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- Accountability by patient in exchange for drug e.g. to provide data, complete visits / assessments
 - Need to define who needs the data, who are the “necessary people”?
 - Two circles of knowledge:
 - Identifiable for direct feedback by treating clinicians/academics
 - Anonymised for everyone else
 - Lack of trust of pharma companies and concern over industry motivation: where will that data end up?
 - Quid pro quo: data collection means more monitoring, in return for access to drug
 - Information needs to be shared up front on who gets which data
 - Patient (and parent) should maintain ownership of data and have access throughout (the right to see own data)
 - Important to have security in place for data
 - Patient / Physician owned registries (not drug-specific registries) would make the process far more efficient as all pharma companies can use it, no duplication
 - A data obligation to share was expressed by a few participants across the three workshops
 - Except half of Alzheimer’s/Parkinson’s group said it’s difficult to impose
 - Some participants suggested it should be treated exactly the same as a clinical trial

Confidentiality

- Recognition that people’s views on data sharing differ.
- Important to understand what is being shared and with whom (needs to be included in consent process).
- Sharing data for the purposes of individual care is different from sharing data for research or commercial purposes.
- People need to know what protections there are for data storage and data transfer. Lessons from ‘care.data’ were discussed and highlighted as a learning opportunity for moving forward.

Emerging themes Post MAPPs

Pricing and access

License review

- When would the conditional license be reviewed and what point would there be a withdrawal / approval process? Patients would need to be informed of this up front, but also on a continuous process

Cost

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- De-risking the process for companies might also
 - Lower the cost
 - Allow them to recoup costs earlier
 - Concern that the NHS would incur greater costs by subsidising/incurring the cost of a trial

Drug Access

- Patients were concerned about equality of access, using postcode lotteries and ‘well-informed parents’ as examples. Everyone should have equal access to treatment opportunities
- Reimbursement was highlighted as an access barrier, often leading to a delay
- Withdrawal of a drug, after an individual appeared to have been getting a benefit (e.g., on a trial) was a particularly emotionally difficult issue
- Parents in particular felt that more continuous feedback, and gradual information about e.g., disappointing trial results would help lessen the blow if drugs were subsequently withdrawn.
- The iterative nature of MAPPs was attractive in this regard.

Reimbursement

- Participants acknowledged that there is a role for NICE in fair allocation of drugs, but some said that it is unclear what the HTA’s want in terms of data, or what the economic model should be
- In the current system, delays between approval and reimbursement decisions are difficult for patients to accept,
- MAPPs was seen as a hope to reduce delays in reimbursement
- Having a drug shown to be efficacious but then not being able to get it on price grounds would be unacceptable to patients
 - They see MAPPs and the early dialogue generated as a way to get around that
- The idea that the global system beyond the UK is important with a need to explain the context of what happens in different countries with respect to approval, pricing and MAPPs
- Also concern that UK only initiatives may not generate sufficient numbers
- Confidence in process might be increased by link to EU pilots

Appendix 3

	Capacity Who collects data, time and budget considerations	Capability How is data collected, expertise and knowledge considerations	Culture Incentives, perceptions, ethics and legal considerations
Organisation Primary care, clinical trial hubs, regulators, payers, industry, third party data stewards			
Systems Databases, software, types of data, integration across sites/data types, data analysis, digital healthcare			
Individuals Clinician, Nurse, Allied Health professional, Patient (inc. family member)			

Table **Error! Main Document Only.** Multi-level Structural Matrix

Healthcare professionals	Industry	Innovation centres	Association groups	NHS	HTA
Dementia research groups in Oxford, King's college London, UCL and Nottingham	GlaxoSmithKline – Salford lung study	Cancer intelligence unit (PHE)	Cancer Research UK	NHS England	National Institute for Health and Care Excellence (NICE)
Cardiology/ George Institute, Oxford	Price Waterhouse Cooper	FARR institute of health of health informatics research	Nuffield Division of Clinical Laboratory Sciences	Nuffield department of orthopaedics, Oxford	Medicines and Healthcare Products Regulatory Agency (MHRA)
Cardiology, Leeds University	Aparito		Association of British Pharmaceutical Industry	Department of Oncology, Oxford	
			Wellcome Trust	Oxford University Hospitals- NHS trust	

				Nuffield department of medicine, Oxford	
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Table 2 Multi-stakeholder expert interviews