MEPs’ Briefing Paper
2014-2019 Legislature
Contents

Personalised medicine in Europe...............................................................page 3
The legislative labyrinth.............................................................................page 4
Clinical trials...............................................................................................page 5
Personal data protection............................................................................page 6
In vitro diagnostics regulation.................................................................page 8
Medicines Adaptive Pathways to Patients (MAPPs).................................page 10
Rational use of resources...........................................................................page 11
Translational research...............................................................................page 12
Real-world evidence..................................................................................page 13
Data-driven economy................................................................................page 14
Education of HCPs....................................................................................page 16
Affordable and sustainable access to Personalised Medicine innovation....page 18
About EAPM...............................................................................................page 20
Personalised medicine in Europe – the way forward

This document aims to underline why top-level policymakers should work in tandem with EAPM and its stakeholders when formulating decisions and direction regarding health in the EU.

EAPM is striving to move the cause of personalised medicine (PM) forward and believes that the new Parliament (and Commission) are in a unique position to push the health agenda further down the road to giving the right treatment to the right patient at the right time. A one-size-fits-all philosophy can no longer work in EU healthcare.

There is an urgent need to move into a new era of innovation and there has never been a better time, given the extended powers bestowed upon the Parliament by the Lisbon Treaty.

One of the basic tenets of the EU is that of equality but, when it comes to healthcare for its 500 million citizens, this is patently not the case. In most areas of health the goal of equal access to the best care and medicines available has yet to be reached.

Among our key aims at EAPM is to use various forums to impress upon you, the policymakers and lawmakers, the need for a more modern approach to healthcare and to provide a platform through which you can hear opinions, suggestions and advice formed by consensus from all stakeholders in the area of PM.

Clearly, one issue affecting politicians today is that almost every stakeholder in healthcare claims to represent the patient. This poses a dilemma in the sense that there are often varying viewpoints. This inevitably leads to a certain degree of confusion and, in some cases, a lack of action or an unnecessarily slow reaction.

Examples include the fact that the Clinical Trials Directive took a decade to revise and the Data Protection regulatory measure led to more than 4,000 amendments. To counter this, EAPM is working tirelessly to build consensus in order to send out a strong and clear message to you, our policymakers, at the highest level. Cohesion and clarity are key.

Politicians will undoubtedly benefit, as will society, from a ‘one-stop shop’, allowing you to hear the consensual viewpoints of all stakeholders and organisations, whether they be patients, clinicians, academics, researchers, industry representatives or, indeed, your fellow policymakers and lawmakers.

It is vital that, in the pursuit of a healthier and thus wealthier Europe, policymakers take part in these forums as, without dialogue and a two-way street, ideas can be lost, confusion may reign and the roadmap to success may lead in the wrong direction. EAPM aims to act as a compass for that roadmap.

EAPM strongly believes that politicians need to have a point of reference concerning policy issues where it really counts. And that is at the stakeholder/implementation/practical level. EAPM provides a platform that brings stakeholders together with a view to achieving a holistic and measured approach to the many challenges and barriers facing us today.

Among these are the establishment of agreed standards of best practices in many varied arenas including (but not exclusive to) biobanks, evaluation of biomarkers, plus the collection, storage and exchange of Big Data (taking into account ethical and ownership concerns). We also need to establish smaller, more-targeted clinical trials and decide how they can be successfully implemented. And we need better, more-modern training for clinicians in new methodologies in order that they can more effectively put the patient at the heart of his or her own treatment and the decision-making process.

Further to this, we need to ensure that there is a linkage – a horizontal methodology - across all key policy areas that involves and encompasses a single approach. For example, the definition of ‘informed consent’ should not vary from one area to the next nor should it vary from Member State to Member State and, thus, healthcare system to healthcare system.

EAPM maintains that none of the above issues can be tackled successfully without stakeholder knowledge, involvement and advice. Nor can they be tackled without yourselves and a firm commitment from all of us to create a healthier Europe for this generation and those to come. The time to act is now.

EAPM refers you to its ongoing STEPs campaign (Specialised Treatment for Europe’s Patients), which calls on decision-makers to commit to the following STEPs for 2014-2019:

- **STEP 1**: Ensuring a regulatory environment which allows early patient access to novel and efficacious personalised medicine
- **STEP 2**: Increasing research and development for PM, while recognising its value
- **STEP 3**: Improving the education and training of healthcare professionals
- **STEP 4**: Supporting new approaches to reimbursement and HTA assessment, required for patient access to PM
- **STEP 5**: Increasing awareness and understanding of PM

EAPM firmly believes that achieving these goals will improve the quality of life for patients in every country in Europe.

David Byrne, former European Commissioner for Health
Helmut Brand, President of EHFG
Denis Horgan, EAPM Executive Director
Through the legislative labyrinth: Pathways to a healthier EU

The field of regulatory affairs in the European Union is by its very nature a complex one. Perhaps nowhere more complex than in the arena of health – and certainly extremely complicated when it comes to legislating for the exciting advances and growing expectations being brought about by personalised medicine.

The issues and rules surrounding, for example, in vitro devices and data protection are labyrinthine. Yet they need to be addressed swiftly and effectively if we are to be able to give the right treatment to the right patient at the right time, while at the same time, offering every European equal access to the best treatment available.

There are 28 Member States and the welfare of 500 million citizens to consider, plus so many disciplines, industries and other stakeholders involved that it is often a struggle for legislators to formulate regulations (and even definitions, as we will see) that are satisfactory for all, are up-to-date and progressive, and do the job they are supposed to do. This despite the best efforts from all involved.

For example, as alluded to above, the definition of ‘informed consent’ differs in the EU’s Clinical Trials Directive and its Data Protection Directive. Readers may very well ask how this can be the case. Clearly, just by that example, there needs to be more – and more efficient - linkages between different legal dossiers across the European Commission to ensure consistency in such important areas.

On the topic of the Data Protection Directive (which received thousands of amendments) it is clear that data relating to individuals are fundamental to modern health research. Its processing is vital for clinical trials and observational research performed by industry and academia.

Data protection regulations must enable patients and the public to benefit from the advances of health research by creating a legal framework that strikes an appropriate balance between facilitating the safe and secure use of personal data in health research and the rights and interests of individuals.

It has been argued that that the processing of data for scientific research purposes is ‘not as urgent or compelling as public health’. But, since progress in healthcare is impossible without health research, is this really logical?

Clearly, despite all the legislation, there still needs to be a middle ground discussed and agreed.

There are certainly ways to make things easier and more efficient. One of the issues noted by EAPM is that there is insufficient collaboration between all stakeholders currently operating within their own ‘silos’. This is a major problem in many areas of health generally, and PM in particular, covering everything from education to information sharing, and from authorities deciding patient access to the need for one, clear voice to communicate with legislators and much more.

It is also a fact that much legislation tends to be reactive rather than proactive. Again, with better collaboration between all involved stakeholders it will be possible to foresee potential problems that could occur down the line, rather than acting in an ad-hoc manner if and when these problems do occur.

In the fast-moving area of PM with its cutting-edge science it is already, and will become more, vital that stakeholders collaborate openly and effectively. This should ensure that regulations and legislation covering, for example the new, smaller clinical trials required to make PM work effectively, the huge practical and ethical issues surrounding Big Data and data protection, and the necessary standards for biobank samples and in vitro devices are common, understood and enforced across the EU.

Clinical trials and medical devices certainly need to be high on the political agenda. There are many legal aspects to clinical trials and, in some Member States, there are conservative laws that make treatments and trials difficult to conduct. EU legislation often seems to be moving towards this conservative style. There is undoubtedly a need for common European health legislation as much as possible, but it must be the right legislation. Experience has shown that having separate rules in every Member State does not work, for a variety of reasons.

It often leads to an R&D environment that is not competitive, slows the innovative dynamic and ultimately represents a barrier to the emergence of effective therapies for untreated disease.

EAPM is working hard to promote integration, collaboration and dialogue among each and every stakeholder in the field of PM. The Alliance believes that it can help mould legislation offering the right laws, in the right place, at the right time. Once achieved, this will allow us all to work more quickly and more effectively towards creating a healthier – and thus wealthier – European Union.
Clinical trials improvements should not be undone by data regulation

The clinical trial regulation published in the official journal of the EU in May 2014 is a perfect example of how legal frameworks can rapidly be improved when legislators work hand-in-hand with all stakeholders and supported by the results of several impact analyses.

The decision to revise the framework came only eight years after the implementation of the previous legislative piece as it was held responsible for the 25% drop in the number of clinical trials in the EU. The new regulation has been proposed and adopted in less than two years.

It makes the clinical trial framework more efficient, better adapted to international trials, it reduces bureaucracy and, thus, unnecessary costs.

It also consolidates patient safety by implementing a single submission portal, coordinated assessment that embraces all aspects of the trial including ethics and by introducing a risk-based approach for trial management alongside centralised safety reporting.

But the greatest achievement of the new regulation is indisputably the increase of transparency in clinical trials. Indeed, the regulation makes the EU database publicly available (this database contains the information on clinical trials and later provides the summary of results. It also provides access to the summary of trial results shortly after the end of experimentation (rather than later).

Going further, as a result of debates in the Parliament, the regulation instigates data sharing and mandates the Commission to produce technical guidelines for data sharing between sponsors (to be performed on a voluntary basis).

The need to enable public scrutiny of clinical trial results, including the possibility to re-analyse the date independently to corroborate published results, were pointed out in debates to be both evidence and a moral duty.

Through these important measures the EU will be able to:

- Provide feed-back on trial results regardless of whether these are positive, negative, or inconclusive, or if the clinical trial could not be completed (providing the main reasons for this), and provide the scientific community with essential background information to foster the next generation of clinical trials;
- Enable independent re-evaluation of the results of pivotal clinical trials or any other clinical trial requiring such independent re-evaluation.

However, EAPM wishes to impress upon MEPs that the Data Protection Regulation in the version voted on by Parliament in April may severely hamper data sharing and therefore prevent public scrutiny and independent re-evaluation of results. Indeed, the insistence upon specific consent will require specifying upfront which individuals and organisations will have access to the data.

At the time of data re-evaluation by independent experts access to the data may be refused as they are not specifically mentioned in the consent. Recontacting participants to seek additional consent at that stage may not only be unpractical but, in some instances also unethical or simply impossible.

Further to the need for public scrutiny and transparency, the regulation recognises the importance of maximising the use of already collected data for medical, natural or social sciences research purposes. It allows for “one time consent” obtained prior to the start of clinical trials to legitimise its future use (provided research is ethically approved) for the sake of patients and scientific progress.

As it stands, the draft data protection regulation would make this re-use of data impossible in many instances for the same reasons it will hamper transparency. Researchers will simply not be given access to this data, even if their research is ethically approved. Such a situation would be unethical in itself as it would result in the unnecessary exposure of individuals to prospective interventions - and the risks that go with them - even though the information could have been obtained using already existing data with no risk to patient safety.

In conclusion, EAPM would like to congratulate Members of the European Parliament, specifically those having contributed to the clinical trial regulation, for the excellent work they have done. Yet the Alliance also urges MEPs to reconsider data protection rules applicable to scientific (and, in particular, to medical and health research), by taking into account its international nature in order to support rather than hinder the transparency and data sharing that is strongly defended in the clinical trial regulation.
Data Protection Regulation: Keeping Health Research Alive

The Spring of 2014 saw the European Parliament vote on an EU proposal for a General Data Protection Regulation (DPR), which is currently being negotiated among the institutions. Once the text has been agreed, it will set the rules for handling personal data in the 28 Member States.

This regulation will rule on aspects as different as personal information shared through social networks, client profiling for marketing purposes as well as health research, which is already heavily regulated.

Since the vote, the European research community has expressed major concerns with the proposals and their potential impact on research.

All EAPM stakeholders and the larger medical and scientific community feel that this text, if finalised in its current form, will severely harm research, may become a barrier to achieving optimal transparency in medical and specifically clinical research and could make clinical trial data sharing practically impossible.

Parliament defended the current text on the basis of article 8 of the charter of fundamental rights of the European Union, which guarantees the adequate protection of personal data for all EU citizens. However, article 13 states that scientific research shall be free of constraint, while article 35 guarantees access to healthcare.

EAPM believes that the current text as applied to health research does not pay enough regard to articles 13 and 35 as the result will be a serious constraint on scientific research and will prevent or slow down research and innovation to such an extent that Europe would not be able to guarantee the quality of healthcare its citizens are entitled to.

Modern healthcare is based on evidence and this evidence comes from data. Therefore, data relating to individuals are fundamental to modern health research. The processing of personal data is vital for clinical trials and observational research performed in industry and academia.

These considerations are even more pertinent with regards to personalised medicine. The ability to use personal data relating to health is central to realising the promise of PM.

Currently, not enough is known about the biology of diseases or why some individuals benefit from a treatment while others do not. A lot of this knowledge can be gathered by analysing and linking already available data, without putting patients at risk of intervention.

EAPM believes it is vital that our doctors have access to the best information and diagnostic techniques available. Today's emerging technologies, such as analytics tools for ‘Big Data’, can help healthcare professionals improve diagnoses and reshape the way medicine is practiced.

Health research may require the use of anonymised, pseudonymised or identifiable personal data. The first of these is outside the scope of the Regulation and we encourage regulators to take a pragmatic, risk-based approach to assessing anonymisation. The use of identifiable data is on occasion necessary though clearly its use should be limited to exceptional circumstances.

Pseudonymised or key-coded data cannot directly identify an individual, but are provided with an identifier that enables the data subject’s identity to be reconnected to the data by reference. These data also fall under the Regulation.

The way pseudonymised data are generated and managed will make an inappropriate identification either unlikely or rather impossible, which would further support a risk-based approach rather than one size fits all.

We should ask ourselves the question that if we want our patients to have the latest medicines and diagnostics, why would we prevent them taking benefit from the analytics that will tell us which of these advances will work for which patients? Important examples include work done in the past to control
the HIV epidemic, understand vaccine safety in children and work for into the neurodegenerative diseases of ageing.

Health research is conducted within a robust ethical framework with safeguards supported by internationally recognised guidelines. In most European countries, it is the mission of Ethical Committees to ensure patient rights and privacy are respected. This means that an individual’s data are only used in research when this is proportionate to the potential benefits for society as a whole. Ethical Committees also focus in particular on the nature and relevance of patient consent.

State-of-the-art procedures for the safe processing of personal data have been developed by the health research community to protect the privacy of individuals participating in research and minimise the risks of identifying individuals where this is not necessary. These technical and organisational procedures build on the long-standing experience of many European centres of excellence for data processing.

It is crucial that the DPR takes into account these existing safeguards and procedures to create a legal environment that promotes the interests of data subjects while providing EU citizens with better healthcare resulting from advances made by the health sciences.

It is challenging to produce legislation with a broad scope that protects citizens while taking into account the needs of different sectors. Personal health data comes from a multitude of sources including individual patient records, clinical research recruitment, biobanking and patient-generated information: all of these data are valuable in their own way.

Despite these challenges, EAPM urges the legislators to recognise the societal benefits of health research and existing safeguards in this area, and to produce a DPR that protects the future of health research in the EU and focuses on how we can construct an ecosystem for health data that advances research and healthcare while providing the necessary reassurance to citizens about how their data is being used. We believe that the current text falls short in a number of ways:

- It requires that subsequent data uses be compatible with the original purpose for which the data was collected, thus potentially preventing access to valuable existing data sources and closing the door of data transparency and data sharing (as the scope of secondary use of data, though legitimate, may be well considered different from the original purpose and patients may no longer be around to express their will)

- It invites Member States to introduce exceptions to EU approaches yet we need to move towards greater alignment of data protection practices

- It introduces a criteria of high public interest for assessing what research should be permitted and disregards the role that Ethics Committees already play in this area

- It proposes consent requirements when it is well-accepted that there are many situations where consent is unobtainable or where seeking consent would undermine the feasibility of the research

A range of safeguards are already used to minimise the risk of re-identification from pseudonymised data in research and instances of breaches have been very rare. Within the research area, as well as recognizing the different types of data that are needed, it is necessary to recognise and build on our existing experience of consent.

Resources would become very difficult, or impossible, to run if consent (specific and explicit) for processing had to be sought for each research project. Generally speaking, including an option for ‘one time’ broad consent in the DPR is a step in the right direction, but an exemption from consent will still be needed in some circumstances, such as when data is being used from population-based disease registries. The EU should support a process of improving alignment between national practices, while preserving existing flexibilities for Member States.

Clearly, citizens need to be informed about the use made of their data, when they wish to be informed. However, the legal obligation needs to be proportionate and advances in communication technology should be considered to bring together needs and realities of health research and privacy. Accountability should go hand-in-hand with flexibility for re-use of data.

Provision of simplified use of pseudo-anonymized data, the possibility to formulate an exemption from the obligation to collect consent and the obligation to put the appropriate oversight of health research in place are the essential elements of the system.

The EU regulation should also aim to better coordinate and facilitate the international research (within and outside of the EU) by clarifying laws applicable in each case and, similarly, to the coordination applicable to international clinical trials. Such a provision will reinforce and harmonise measures already in place while fostering research and innovation.

Therefore, EAPM strongly urges MEPs to ensure that the Regulation is appropriately amended to permit the primary and secondary use of data for health research purposes bearing in mind the safeguards already in place.
Proposal for a regulation on in vitro diagnostic medical devices

The revision of the EU In Vitro Diagnostics Directive presents an opportunity for strengthening the current approval system for IVDs for the sake of patient safety, competitiveness and innovation. To ensure that the final outcome of the ongoing discussions is a well-performing approval system, several points specific to IVDs should be considered carefully.

IVDs, especially companion diagnostics, play an essential role in personalised medicine (PM) and the patient-healthcare pathway. As non-invasive tests used for diagnosis, screening, assessing predisposition and monitoring, IVDs do not treat patients; instead, they rely on biological samples, including blood, urine or tissue, to provide a specific set of data regarding an individual’s health status. With this in mind, there are certain intrinsic characteristics of IVDs that distinguish them from medical devices and pharmaceuticals.

Within the IVD sector, companion diagnostics consist of highly innovative and precise tools that necessitate special consideration of these integral components of the further development of PM.

Defining companion diagnostics

Companion diagnostics provide the potential to more effectively treat patients by targeting therapies and avoiding ineffective treatments that may cause harm. This important and unique role within PM strongly links companion diagnostics to their counterpart companion drug – simultaneously distinguishing them from other IVDs – and has been acknowledged as such by the European Commission and Parliament in the discussions on the IVD Regulation, leading to the inclusion of a companion diagnostics definition in the proposal.

‘Companion diagnostic’ is a device specifically intended for, and essential to, the selection of patients with previously diagnosed condition or predisposition as suitable or unsuitable for a specific therapy with a medicinal product or a range of medicinal products.

Acknowledging the specificities of companion diagnostics is a significant step in terms of developing a well-suited approval procedure that will foster innovation and bring the needed diagnostic tools to patients.

Conformity assessment for companion diagnostics

As regards the assessment of companion diagnostics as proposed by the European Commission, key concerns include:

- The degree of review by the European Medicines Agency (EMA) is not defined, neither in timing nor desired outcomes;
- Interaction between EMA and notified bodies is not clear; and
- The level of expected evidence for demonstrating the ability of the companion diagnostic to appropriately select patients is not clarified.

The European Parliament has further expanded the control of companion diagnostics, by including the mandatory development of Common Technical Specifications (CTS), which would outline the prerequisite targets and expectations that these devices must satisfy.
The CTS would be developed by regulators with input from EMA, physicians, patients, notified bodies and manufacturers and would provide a high level of detail and transparency of prerequisite safety and clinical requirements.

While the Commission’s original proposal would produce unnecessary administrative burdens, especially for small and medium enterprises, CTS would cut down on time and red tape by providing clear technical requirements that companion diagnostics need to meet whilst ensuring a high level of safety and performance.

**Clinical evidence**

A critical consideration for studies conducted on IVDs is that they never interact directly with patients and, consequently, any risk posed to patients – cemented by the new risk-based classification system – would stem from the information provided. With this in mind, much of the evidence generation that is required of IVDs can actually already be gathered in the developmental phase with samples obtained from biobanks.

However, as companion diagnostics are linked to the choice of a specific therapy for a patient, they present a unique case and necessitate specific requirements, including more stringent oversight and extended scientific validity.

This is appropriately accounted for in the Commission proposal and establishes the means for collecting clinical evidence and conducting performance studies that provide safety, efficacy and efficiency distinctly for companion diagnostics and other IVDs.

**In-house exemption for companion diagnostics**

Expanding the in-house exemption, which allows for tests to be developed and used within a single health institution without having to satisfy all of the requirements of the proposed Regulation, to companion diagnostics raises some concerns.

Different from other tests, companion diagnostics are subject to specific requirements in order to demonstrate that patients are appropriately selected for the use of life-saving therapies.

As such, the clinical evidence requirements for companion diagnostics are substantially higher than those for most other IVD assays, thus explaining why companion diagnostics should only be permitted to benefit from the in-house exemption in instances when no equivalent test is available.

**Marketed IVDs and new clinical evidence**

Tests that check for the presence or absence of specific biomarkers – measurable indicators such as cells, molecules or hormones that indicate the presence or severity of a disease state – may consist of IVDs that have already been approved for market access. Often when the tests were made available for the measurement of a biomarker, there was no known clinical correlation to a disease.

As these are discovered and evidence is formulated to indicate treatment possibilities, clinical trials on these therapies – not the test identifying biomarkers – should be conducted according to the Clinical Trials Regulation, not the IVD Regulation.

**Gene sequencing and companion diagnostics**

The potential of personalising treatments offered by gene sequencing of patients or their diseases (e.g. tumours) may enable scientists to acquire more information on the severity of a disease, as well as distinguish between those patients who will benefit from a treatment and those who will not.

As such, sequencing is a validated method; one which can be corroborated based on samples and extracted data. Any subsequent treatment methods based on the information would be subject to regulation under the Clinical Trials Regulation and should not fall within the scope of the IVD Regulation.

**Transition period**

The five-year transition period for IVDs, as proposed in the text, is needed for manufacturers to be able to fully comply with the various new requirements and place all of the necessary procedure in place.

Anything less than a five-year transition is simply not feasible due to the comprehensive changes required of manufacturers and importers, Notified Bodies, Competent Authorities, reference laboratories, the European Commission and other organisations.

The need for a five-year transition period was demonstrated in Australia, when the implementation of a similar legislation required an extension from an original three-year transition period to four years and, as of 29 May 2014, to five years.
Medicine’s Adaptive Pathways to Patient’s (MAPPs)

Overview – MAPPs in Europe, a Stratified Approach

Medicine’s Adaptive Pathways to Patients, or MAPPs, provide a limited commercial marketing authorisation for a well-defined stratified population that is likely to respond based on available diagnostics for therapies with a high level of efficacy and safety.

Simultaneous randomised clinical trials (RCT) are also run to validate additional clinical endpoints outside the initial launch population. In this way, the population targeted by the therapy will evolve and ‘adapt’ with the evolution of the evidence package. Ideally, much of this confirmatory evidence would be obtained via ‘real world’ observation.

According to the EMA, this approach “is intended to maximise the positive impact of new medicines on public health by balancing the need for timely patient access with the importance of providing adequate, evolving information on a medicine’s benefits and risks”.

MAPPs and its associated areas of applied research funding will be a major area of focus across the EU for the next five years. EMA has instituted a MAPPs pilot project under a ‘safe harbour’ environment to allow the exploration of the strengths and weaknesses of all options for development, assessment, licensing, reimbursement, monitoring, and utilisation pathways in a confidential manner and without commitment from either side.

IMI2 will also have many projects related to research aligned with MAPPs under Horizon 2020.

The core barriers to MAPPs are:

- Key Member State stakeholders (patients, regulators, practitioners, industry, HTA/payers) must be aligned at the design phase of a ‘MAPP’ and agree on the evidence package for early approval and re-assessment;

- There is a need for a better understanding of patient’s and payers’ willingness to operate with greater uncertainty driven by the release of needed therapies with less evidence at the initial launch;

- The IT infrastructure and processes to provide the necessary evidence base using real world data do not exist in most of Europe;

- If the 28 Member States in Europe do not accept the value of MAPPs, there will be no way to ultimately pay for new medicines that are licensed by EMA to enter the marketplace;

- There must be willingness by national regulators to address a flexible pricing structure that responds both upwards and downwards based on the evolution of data and knowledge gained in the course of a MAPPs development plan.

Potential Benefits

MAPPs is a move away from the traditional binary ‘on/off’ approach to the approval of new medicines as practiced in the RCT. Regulators must accept that an RCT is not a guarantee of:

- Statistical certainty;

- A predictable safety profile, or;

- The actual performance of a new therapy in the real world. MAPPs should also incur fewer adverse events and less toxicity, as the limited initial license will be focused on those most likely to respond. It can also radically reduce the time to market for new therapies, relieving pressure on the exponentially increasing costs of RCTs.
Rational use of resources to ensure personalised medicines are affordable

With personalised medicine, we are on the cusp of a revolution in healthcare. But whether we can support innovation – and afford it – will depend on how smart health systems are at allocating resources in the right way.

A range of technological and scientific advances are leading to more and more personalisation of treatment. As our understanding of disease improves, along with our ability to profile patients according to their individual genetic and other characteristics, the pharmaceutical industry is increasingly able to better target new therapies to specific groups of patients that are likely to benefit.

This should lead to multiple advantages, including improved health outcomes, better tolerance and fewer side effects. But is society able to pay for personalised medicine? Judging by the current debate about pharmaceutical pricing, it seems that ensuring a sustainable economic model that allows these medicines to be produced, profitably, but in an affordable way for health systems may be a challenge.

The problem is straightforward. Producing medicines has not become any cheaper. If anything, the opposite is true with development costs rising almost exponentially in recent decades. The latest figures suggest the average medicines are still taking over $1 billion and around 12 years to bring to market.

At the same time, the size of the market on which private sector companies are able to recoup their costs has become much smaller – a natural result of increasing personalisation of treatment, that is likely to continue in future.

So does the fact that it’s more expensive to produce medicines for fewer people mean that medicines are (or will be) unaffordable for healthcare systems? The answer is ‘no’ – at least not necessarily.

The key challenge for health care systems to manage medicines spending – whilst also delivering on innovation - will be to ensure ‘rational use’. Where it is possible to treat a patient to target on an older, cheaper medicine it should be done. But if a patient needs a more modern treatment, access should be provided at reasonable prices that reflect both the added value and the volume across the market – with low volume treatments naturally commanding a higher price. Getting this balance right ensures that everyone wins. Existing evidence shows clearly that countries actively managing rational use have lower spending growth for medicines as a whole – and therefore more potential ‘headroom for innovation’.

Across the OECD, medicines expenditure growth lags behind that of overall healthcare spending. The reason for this is that, despite the growth coming from new products, the off-setting savings derived from the loss of exclusivity of several major older products lead to reductions in price and, hence, savings that can be redeployed.

All this is not to say that we don’t have a challenge. Savings that accrue in one part of a health system rarely get efficiently redeployed where costs are rising. But it is an important message that the challenge of making health systems sustainable is not simply a debate about price or cost, it’s also about how resources get allocated and about how we ensure an efficient use of the right technology at the right time.

Advances in information technology offer the potential of proving health system managers with a more ‘information rich’ environment on which to base decisions. Ultimately, this trend will help support a more integrated approach to care and should improve efficiency. We’re not there yet of course – but we have a better idea about where to focus policy effort. Genuine efficiency can support rather than stifle innovation. That’s what EAPM seeks to promote.
Translating research into clear patient benefit

European researchers have been at the forefront of major scientific discoveries in many aspects of health, in areas as diverse as cancer, cardiovascular, genetic and infectious disease, but the key challenge is to translate this knowledge and expertise into medical advances that improve outcomes for European patients.

EAPM believes there is an urgent need to develop and adequately resource a patient-centred European Translational Research Platform that ensures the efficient translation of research promise into innovative care for the EU’s patients.

Translational research is a key enabler of the European Union research effort and represents the conduit through which European discovery science can be converted into new diagnostics, treatments and products that benefit citizens and society.

Personalised medicine (PM) holds enormous promise and is already delivering therapeutic benefit, particularly in diseases such as cancer, but its promise can only be realised by a harmonised European research agenda that enables efficient and effective translation of scientific innovation, underpinning practice-changing clinical advances for our patients.

Enablers and barriers

While Europe continues to produce excellent science that provides an increasingly informed insight into the role of biology in health and disease, our ability to translate this into clear patient benefit is undermined by the structures and regulations currently in place at national and European levels.

A fragmentation of the research effort across Europe, a pressing need for comprehensive stakeholder engagement, allied to the lack of a clearly defined roadmap for translation of research discoveries for clinical implementation, are hampering the delivery of a PM agenda that has the potential to deliver both health and socioeconomic gains for Europe.

Embedding PM into European healthcare systems is a key objective of EAPM and the Alliance urges Parliamentarians to:

- Commit to the development of a European Translational Research Platform that enables the efficient translation of research discoveries to innovative diagnostics, therapeutics, products and processes that will benefit patients, industries and societies. Such a platform should have the following characteristics:
  - A link between infrastructure in omics, pathology, biorepositories, big data, biomarkers, diagnostics, imaging, drug development etc
  - A coalition of expertise across the translational research continuum in the above areas/domains so that it can effectively deliver translational solutions but also engage with funders/payers and the European Commission etc
  - The provision of an academic-industry-clinical-patient partnership to drive research from concept to reality
  - The embedding of personalised medicine in European Healthcare systems
  - Support for the designation of specific funding mechanisms within the EU Horizon 2020 Research budget to drive the effective translation of European scientific excellence
  - The enablement of active cooperation between all relevant stakeholders to remove the barriers (structural, regulatory, etc) that hamper the development of a coherent European Translational Research Platform.
Real-world evidence: Barriers and opportunities

What is ‘real-world evidence’?

In healthcare this is a simple concept – harnessing various health data in real time to help make faster and better medical decisions. RAND Corporation in their recent report Assessing the Real-World Data Policy Landscape for Health and Healthcare in Europe defines real-world evidence as, “an umbrella term for different types of healthcare data that are not collected in conventional randomised controlled trials... including patient data, data from clinicians, hospital data, data from payers and social data”.

Real-world evidence is crucial to the implementation of adaptive clinical trials. Medical Adaptive Pathways to Patients (MAPPs) are currently being tested in a European Medicine Agency pilot project, which calls MAPPs “a prospectively planned process, starting with the early authorisation of a medicine in a restricted patient population, followed by iterative phases of evidence gathering and adaptations of the marketing authorisation to expand access to the medicine to broader patient populations”.

It is the ‘iterative phases of evidence gathering’ that ideally will utilise real-world evidence to more accurately detect patient responses to new therapies in real time.

There are currently upwards of 17,000 health ‘apps’ being released annually, and the US Food and Drug Administration anticipates 500 million users by 2015. Many of the emerging new technology platforms, particularly advanced mobile phone health apps, have the capability to not only provide real-world evidence, but also run simultaneous ‘head-to-head’ efficacy trials against existing therapies.

For example, the company Handle my Health has the ability to aggregate multiple health apps into one data packet, and then send these to the UK’s MHRA for real-time verification of data, potentially under the UK’s Early Access to Medicine’s Scheme.

Thus, mobile health apps also have the opportunity to solve the issues of data interoperability, as a de facto data standard emerges conforming to iPhone or Android platforms. These real-time datasets could then be transmitted as standard web XML files to any database, anywhere.

Several national health databases provide the opportunity to search, identify, and target anonymised patient data that can drill-down to the practitioner with integrated real-time updates of national health records.

Current barriers to the implementation of real-world evidence:

- The required data infrastructures do not exist everywhere in Europe
- The data collection systems are not harmonised and many of the most successful implementations are customised locally
- The technology evolves more quickly than regulation can adapt
- Regulatory authorities at the Member State level are not currently equipped to base decisions on real-world evidence
- The ‘Right to Be Forgotten’ data protection legislation may compromise the ability to use real-world evidence in clinical development
- Next-generation healthcare harnessing real-world evidence will be increasingly multisectoral and multidisciplinary, challenging the current status-quo of regulatory oversight

Regulatory needs for the implementation of real-world evidence:

- Regulators should facilitate health information technology implementations that are driven by current best practices with the understanding that all processes will need the ability to adapt rapidly to evolving technologies
- EU regulators should support projects that investigate the use of real world data for approval and reimbursement of new therapies at the Member State level
- The opinions of patients with conditions for which there are currently limited treatment options must be incorporated when considering alternative evidence bases such as real-world data
- Data protection legislation should be reconsidered with regards to healthcare, as it may place Europe at an international disadvantage for the use of real-world data
- The EU should allow for a wide scope of eHealth and mHealth applications without over-regulating the sector, similar to the ‘light touch’ approach of the FDA with regards to mHealth.

Programmes such as IMI that support a multidisciplinary approach/dialogue are vital to implement real-world evidence based development in Europe.
Personalised medicine and a European Data-driven Economy

With the aim of supporting a European Data-driven Economy, EAPM believes that, by 2020, the EU should endeavour to achieve widespread benefits for citizens and patients from personalised healthcare by defining in 2015, and subsequently executing a Data Strategy for Personalised Medicine.

This strategy aims to create the conditions for the EU-wide exploitation of the entire data stack for personalised medicine. The strategy should consider a 360-degree view of policy enablers to ensure a comprehensive analysis of all the interrelating decisive factors in play for the development and adoption of Big Data for personalised medicine in Europe.

A Lighthouse Initiative on Personalised Medicine

The internet is a vast worldwide decentralised network of billions of different devices that work as a whole because all the nodes of this network speak the same standard protocol (TCP/IP) on top of which email, WWW, voice and all the other services we are used to are built. Imagine that such a linked network of data resources could be established in support of personalised medicine (PM), closing the circle from the citizen to research to clinical care and back efficiently and in timely fashion.

To facilitate this, EAPM calls upon the European Union to focus resources to set up a Lighthouse Initiative on Personalised Medicine which, through Member States and multi-stakeholder collaboration would drive policy, regulatory, research and innovation activities to establish a Europe-wide Data ecosystem for personalised medicine.

The Lighthouse Initiative would not start from scratch, but it would bring a much needed holistic and focused approach to what is a multidimensional challenge. By stimulating collaboration and activities addressing computing infrastructures, data collection, storage, analytics, management, governance, security and privacy these would be put to work to establish a Europe-wide data ecosystem for PM, supporting among other things, domain specific research, medical decision making at the point of care, patient engagement and entrepreneurship through innovative startups and SMEs.

Many nodes of this ecosystem are being developed across Europe and beyond.

New developments on citizen-centric solutions based on mHealth and telehealth are delivering care outside hospital walls whilst capturing more data about individuals’ health, contributing to prevention and care personalisation, and supplying crucial information with the potential to increase knowledge about response to treatments.
This, when cross-referenced with clinical and genomic data, can be used to gain novel insights about the genesis, progression and treatment of diseases.

Big Data for personalised medicine for the benefit of citizens and patients can only realise its full potential after considering its dependencies spanning the technological, regulatory, ethical, organisational and political dimensions.

Thus, it is vital to identify those policies that unleash the power of Big Data and orchestrate a strategy around those that can mobilise stakeholders across Europe.

**Recommended actions**

EAPM invites the EU to:

- Take stock of the regulatory landscape for the protection of personal health data across the EU, with Member States and the Article 29 WP with a view to interpreting and clarifying its application towards Personalised Medicine. Consent approaches should allow data to flow freely, but patients should remain in charge of their data.

- Coordinate an approach with the Member States to streamline the cross-border sharing of EHR data and genomic data for secondary use.

- Analyse and share good practices, identify roadblocks, propose corrective measures and issue EU-wide guidance on issues such as breaking silos of single-use data; facilitating data processing; notifications of breaches of privacy; conditions for international data transfer for biomedical research as well as considering frameworks for data governance that can be applied across Europe.

- Identify the opportunities brought by the adoption of data-derived knowledge in daily clinical operations, including mHealth, and issue a short- and medium-term set of implementing actions, addressing inter alia the adoption of genomic information in clinical care, patient generated health data, medication adherence and pharmacovigilance;

- Step-up the support for initiatives that promote the expansion of technologically advanced, secure, quality-assured and harmonised data registries, their linkage and outreach across the healthcare delivery system actors.

- Focus Horizon 2020 and IMI 2 funds to address some of the domain-specific challenges and advance the state-of-the-art of core technologies at the crossroads of ICT and Personalised Medicine, namely:
  - Development of hardware, software and algorithms to accelerate cost-efficient analytics and visualisation of genetic abnormalities that cause cancer and other complex diseases;
  - Research at the convergence of mHealth, Big Data, Cloud computing, security and anonymisation techniques to meet the requirements of High Performance Computing and data throughput through the life sciences and healthcare value chains;
  - Research on policy implications and new models of ownership;
  - Centres of Excellence for big data science and life science applications of HPC systems, including algorithmical research, software technology and education.

In support of education and training, the EU, patients’ and healthcare professionals’ organisations are invited to collaborate in order to:

- Complement general public health campaigns with specific messaging to broaden the awareness of personalised medicine;

- Provide education that improves health professionals’ ability to involve patients;

- Recognise patients’ rights to seek information about care options;

- Adapt the provision of continuing professional development and training activities;

- Adapt curricula for undergraduate, post-graduate and specialist education;

- Develop training systems that provide for interprofessional collaborative practice and produce interdisciplinary professionals.

- Nurture data-enabled entrepreneurship. The EU is invited to create the conditions for startups and SMEs to derive value from a data ecosystem for personalised medicine. Education and collaboration means better treatment for patients.
Education of HCPs means better treatment for patients

In the changing world of healthcare in Europe, including exciting new developments in personalised medicine (PM), a key element is under-emphasised – namely, the education of healthcare professionals (HCPs).

The true potential of all of the new science, built around genetic profiling and individual DNA, will never be fully realised unless the front-line clinicians have the knowledge and understanding to exploit it.

There is also an urgent need for an improvement in relationships between all key stakeholders in order to develop trust and new partnerships, in order to give clinicians better tools to treat and inform their patients and allow healthcare professionals a better understanding of their patients’ needs.

The modern patient wants to be informed in a transparent, unpatronising and clear way about his or her options and be allowed properly into decision-making with regard to treatment options, taking into account lifestyle and other factors.

The issue of education of HCPs is a major one. It is clear that a great degree of upskilling is already required and, to keep pace with the science, this must be ongoing. Stakeholders need to achieve this together – with agreed standards across the board so that no patient is denied a suitable, virtually tailor-made treatment due to a lack of knowledge or understanding on behalf of the HCP treating and diagnosing him or her.

EAPM believes that, given the advances in personalised medicine in recent years there is now a need to reform how healthcare is delivered to the technology-aware patient.

A key partner in tackling this is the healthcare community and one way to achieve the goal is through increased EU-wide investment in the education and training of HCPs.

In the case of PM the healthcare professionals are all directly related to the integration of ‘omics’ technologies and range from GPs to bioscientists and biostatisticians.

Health is clearly all about patients and potential patients – 500 million across the EU. Each healthcare system within the 28-country bloc features the coming together of one set of stakeholders, a coming together of four major interests – providers, payers, patients and policy.

EAPM has called for action at EU level, saying: “By 2020, the EU should support the development of a Europe-wide education and training of healthcare professionals’ curriculum for the personalised medicine era, by committing to this in 2015. The EU should subsequently facilitate the development of an Education and Training Strategy for HCPs in Personalised Medicine.”
Recommended actions

- Researchers should focus on analysing desired competences in HCPs to ensure a more comprehensive and strategic approach to practising PM. Identifying current and anticipating future skills needs will ensure professionals are properly equipped.

- To avoid fragmentation, universities all over Europe should work together to identify core competences for students and develop matching and transferable curricula. Research should include evaluation of existing university programmes plus the input of various European medical specialty organisations who already have existing European curricula and guidelines.

- The implementation of compatible PM curricula could be explored through partnerships with existing projects such as the European Higher Education Area, which was set up to ensure a more comparable, compatible and coherent system of higher education in Europe.

- Courses should provide awareness of PM’s complexity early in a HCP’s career.

- A network of European experts on Continuing Medical Education on PM should be created to help Member States to move forward. In order to promote harmonisation of education and training, these organisations could team up and incorporate PM in their curricula and guidelines. In order to finance the expert group, synergies with current networks should be explored.

- A rigorous code of conduct should be developed and followed by bodies involved in HCP education.

- Educationalists should be consulted to identify and produce the most effective method of teaching PM, using more interactive, discussion-based teaching methods.

- Educational programmes should take into account not only the technical aspects of PM but also practical, social, ethical and legal issues. The conceptual change that is required of HCPs is substantial and should not be underestimated.

- Awareness and literacy must be enhanced among patients and the medical community.

- HCPs should be provided with good and easy access to the latest developments in a profession-specific portal.

- The gap in communication between HCPs, researchers and industry must be bridged through a robust, networked, knowledge-sharing system into which HCPs, researchers and industry can share information. The system should:
  - Establish and provide multi-lingual, cross-professional information to HCPs throughout the EU;
  - Allow HCPs to query the system based on treatment modalities, patient symptoms, clinical questions, genetic alterations or other keywords;
  - Be populated by a pan-European HTA body, with input from specialty medical societies and patient advocacy groups and regulatory approval within the EU, to evaluate the level of evidence supporting technologies and interventions;
  - Integrate ‘omics, environmental and lifestyle information and guide HCPs through the decision-making process.

- International conferences/meetings on methods and tools should develop standards for accessing technologies and involve all stakeholders. The outcomes of this work should be incorporated into each assessment.

- Communication experts should be consulted on how best to open channels between different HCPs.

- Existing networks should be used to maximise impact such as research networks.

- A European Observatory on HCP Education in PM should be established to:
  - Create a set of competencies required for HCPs which are necessary to practice PM effectively;
  - Develop standards to accredit bodies to provide cross-disciplinary CME in PM to HCPs;
  - Assist in developing best practice guidelines for teaching and practicing PM;
  - Facilitate data-sharing between HCPs, scientists, researchers and industry, and;
  - Provide access to additional publications and educational materials in PM, especially for topics which are still considered investigational.
Affordable and sustainable patient access to Personalised Medicine innovation

Personalised medicine (PM) promises to revolutionise healthcare and has the potential to substantially improve patient care and patient outcomes, while supporting efforts aiming at more efficient healthcare systems.

It uses diagnostic tools to identify specific biological markers, often genetic, that can help assess which medicinal treatments and procedures will work best for each patient. By combining this information with an individual’s medical history and circumstances, PM allows doctors and patients to develop targeted prevention and treatment plans.

However, patient access to innovative PM technology varies dramatically between and within EU Member States. If the potential of PM is to be realised, changes will be necessary in the way medicines are developed, regulated, assessed (HTA) and paid for.

It is necessary to make policymakers and payers realise that investing now in these advanced therapies and technologies, as well as in adequate regulatory and payer decision making frameworks, will be a key pre-requisite to seeing the full potential of PM in terms of improved patient outcomes and more efficient health care systems.

The necessary steps to improve the situation range from better coordination and collaboration models between stakeholders and decision makers at various stages within the bench-to-bedside timeframe and across countries to more sophisticated pricing, reimbursement and funding mechanisms as well as effective forms of utilisation management to address the inherent complexity of PM technologies and services.

EAPM considers the following actions to be necessary:

● Patients are at the centre of the health care process and should be more actively involved in Health Technology Assessments (HTA)

● Ensure that capacity of HTA bodies is allocated to support their engagement in the early and continuous dialogue with technology developers about the evidentiary expectations for new technologies and services, involving other decision makers, stakeholders, and experts as required

● A new and broader definition of value, which explicitly includes the full benefits of PM, needs to be developed and adopted in pricing and reimbursement systems for drugs and diagnostics

● Generating evidence on citizens’ expectations and the wider societal costs and benefits of PM technology and services is a pre-requisite for their successful introduction into routine care

● Additional research should be encouraged to develop and improve evidentiary and analytical methodology and standards that fit the specifics of PM and the needs of decision makers for reliable and generalisable evidence

● Actively back the adoption of support methodology for HTA, appraisal and patient access decision making that helps to ensure that multiple and conflicting decision criteria are recognized and dealt with in a balanced manner

● Strengthen the capability and re-allocate capacity of HTA systems to assess existing, potentially obsolete health technologies and services and to provide guidance for their optimised utilisation

● National HTA agencies should agree on common standards for relative clinical effectiveness assessments and ensure that jointly conducted assessments based on these standards are accepted for use in national patient access decisions
Uncertainty that is present at the time of launch of PM technology and services should be systematically addressed, provided that this is cost-effective and that this can realistically influence future decisions.

Regulatory, HTA, and other decision maker needs for evidence gathered post launch, should be coordinated nationally and as needed across Europe to make efficient use of limited resources.

EU Member States should establish efficient data collection infrastructure to monitor utilisation, effectiveness and other quality of care considerations of PM technology and services under routine care conditions.

Ensure that national pricing and reimbursement mechanisms are sufficiently flexible to accommodate innovative regulatory pathways aiming at earlier access for patients with serious or life-threatening illnesses (e.g. adaptive licensing) without invalidating relevant incentives for manufacturers to engage.

Pricing and reimbursement systems for PM technology should enable price adjustments over time to reflect increases and decreases in value.

Active exploration of the practical feasibility and acceptability of differential pricing for different indications of the same medicine in order to incentivise the optimal development and utilisation of PM technology and services.

Ensure that the use of diagnostic tests without performance evidence is controlled, using a combined approach of regulation and clinical guidance.

Ensure that pricing and reimbursement systems incentivise the continuous development of diagnostic technology and services as well as the respective evidence for their improved analytical, clinical performance, and clinical utility.

Funding and reimbursement decisions for co-dependent personalised medicine and companion diagnostic should be closely coordinated and take place at the same level in the health care system.

Establish a set of principles for international reference pricing mechanisms for pharmaceuticals so that they are no longer major barriers against sustainable patient access in less wealthy EU Member States.

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The European Alliance for Personalised Medicine (EAPM) brings together European healthcare experts and patient advocates involved with major chronic diseases. The aim is to improve patient care by accelerating the development, delivery and uptake of personalised medicine and diagnostics, through consensus.

EAPM was launched in March 2012, as the European discussion on personalised medicine gathers pace. It is a response to the need for wider understanding of priorities and a more integrated approach among distinct lay and professional stakeholders. It works on case studies, education, training and communication to deliver practical policy recommendations designed to exploit the potential of personalised medicine to the full.

The mix of EAPM members provides extensive scientific, clinical, caring and training expertise in personalised medicine and diagnostics, across patient groups, academia, health professionals and industry. Relevant departments of the European Commission have observer status, as does the European Medicines Agency. By bringing together all stakeholders, EAPM’s aim is to help to forge constructive links between the EU institutions and society.

The EAPM Forum brings all members together every 2-3 months to review activity and to direct political strategy. Working groups develop positions on key topics and make proposals and recommendations to the Forum. The secretariat manages day-to-day operations, prepares Forum meetings, and co-ordinates the working groups. EAPM is funded by its members.

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