EBE-EFPIA Personalised Medicine Working Group Manifesto

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Purpose and content of the Manifesto

The EBE-EFPIA Personalised Medicine Working Group Manifesto aims to highlight policy elements that are considered essential to ensure that personalised medicines and their paired diagnostic tests, also called companion diagnostics, successfully reach patients.

The Manifesto consists of three distinct parts, supported by a glossary, addressing the following policy needs:

- **A clear and coordinated process for the regulatory approval of personalised medicine (Part I)**
- **A clear and predictable process for the economic/value assessment of and access to personalised medicine (Part II)**
- **A European regulatory framework that is supportive of innovation – creating a flexible and "forward-looking" regulatory and reimbursement environment (Part III)** – which includes:
    - The use of multi-marker signatures
    - The use of electronic health record systems that facilitate clinical research, ease the collection and processing of real-world data and improve clinical practice
    - Data protection legislation that effectively facilitates the use of "big data" in healthcare research.

For each of the three parts above, barriers as well as related solutions are highlighted.

Part I: A clear and coordinated process for the regulatory approval of personalised medicine

It is essential to clarify the role and responsibility of each player participating in the various phases of bringing personalised medicine (medicinal product and test) to patients. For each of these phases, key barriers as well as proposed solutions are outlined.

1 - Coordination of scientific advice for personalised medicine

Barrier:
The registration pathways for medicinal products and diagnostic tests are independent of each other in the European Union. This is anticipated to lead to a lack of coordination between decision makers, such as the European Medicines Agency (EMA), National Competent Authorities (CAs), Health Technology Assessment (HTA) bodies and Notified Bodies (NBs). Such a lack of coordination could pose a significant challenge for medicine developers and diagnostic manufacturers during the development and registration of the medicinal product and its associated companion diagnostic test.

Solution:
Specific scientific advice procedures should be developed to allow a collaborative approach between the EMA and NBs, taking the positive experience of parallel EMA-HTA advice into account.

2 - Regulatory assessment (including labelling)

Barriers:
The role and responsibility of the EMA or the relevant CA of an EU Member State in the evaluation of the suitability of a companion diagnostic for a given medicinal product is unclear, as stated in the recently adopted In-Vitro Diagnostic Medical Devices Regulation (IVD Regulation – Regulation (EU) 2017/746). It may lead to an unpredictable pathway and delays if there is duplication of work with NBs or conflicting assessments. More granularity is required, detailing how the interaction between the EMA, CAs and NBs will work in practice. The following points highlight key questions related to regulatory requirements throughout the IVD development process:

- The EMA or a CA will deliver an opinion to the NB on the companion diagnostic test and its suitability in relation to the concerned medicinal product. The conceptual elements and their management are unclear.
- How will the assessment or opinion on the companion diagnostic be integrated by the EMA or relevant CA into the formal medicinal product approval procedures and what role is

foreseen for the industry regarding the interactions with regulators, to ensure that concerns or questions are resolved in the most efficient manner?

- What is the mechanism for the resolution of conflict in cases of misalignment between NB and EMA or CA to avoid delay of approval for medicinal product or companion diagnostic?
- What are the regulatory requirements for investigational IVD tests used in the context of personalised medicine clinical trials? Standardisation of investigational IVD requirements is a challenge since the clinical trial application process governing medicinal clinical trials depends on the individual CA in each Member State.
- How will labelling decisions be coordinated between the medicinal product and companion diagnostic? Under the IVD Regulation, in its instructions for use, the companion diagnostic will refer to the International Non-Proprietary Name (INN) of the associated medicinal product for which it is a companion diagnostic. As for medicinal products, precedence of centrally approved products uniformly shows a requirement to use "a validated test". Formal guidance on medicinal products' labels should be developed when a companion diagnostic is used for patient selection (e.g. regarding the appropriate level of description of companion diagnostic test performance needed in the label).
- The pharmaceutical legislation has several provisions to enable accelerated approval and earlier access to innovative medicinal products for patients (e.g. accelerated assessment, PRIME scheme, conditional marketing authorisation, compassionate use, adaptive pathways, etc.) with the possibility of gathering real-world evidence. The independence of the medicinal product and companion diagnostic registration pathways could lead to a lack of coordination and potential delays in the companion diagnostic test registration for medicinal products that make use of an accelerated regulatory pathway.

Solutions:

The EMA's and CAs' new role and responsibility in the assessment of companion diagnostics should be clearly defined and effectively communicated. Furthermore, the EMA's and CAs' assessment of the suitability of the companion diagnostic in relation to the medicinal product must be coordinated closely with the NB to prevent delaying the availability of both the medicinal product and the companion diagnostic.

As part of the assessment, the companion diagnostic test's analytical and clinical validation requirements expected by the NB, EMA or CA must be identified clearly and consistently with each other. This information should be made publicly available or shared through guidance documents.

Furthermore, during early dialogue with the medicines regulators, there should be an opportunity for developers of both medicinal products and companion diagnostics to discuss and agree on a single, integrated development plan with both medicines regulators and NBs. This would allow for the target (biomarker), diagnostic test and medicinal product to all mature together during development. Appropriate guidance should be developed by the EMA to support this process and clarify the performance data that will be requested, together with a procedural timeframe.

As well, adaptive regulatory pathways that can incorporate additional scientific evidence are needed, as they are particularly suitable for biomarker-selected populations. These flexible pathways would allow the updating of the intended use of the diagnostic tests and prescribing information of the medicinal products whenever novel clinical safety and efficacy information becomes available (e.g. new genomic targets).

Finally, the publication of precedents would be helpful in creating additional transparency with regard to review criteria. There is a critical need in personalised medicine for a publicly accessible database that lists all approved medicinal products along with their companion diagnostic test that have been appropriately validated for the relevant intended clinical use. This database should be updated frequently and provide links to publicly available performance data for both the medicinal product and companion diagnostic test. The example provided by the US FDA could be considered for this purpose (link available HERE).

Specific considerations for targeted topics

Four targeted topics require specific considerations: follow-on companion diagnostic tests; in-house testing; clinical evidence of a biomarker; and large genetic panels.

Follow-on companion diagnostic tests:

Barrier:

EU requirements for clinical validation of a "follow-on" companion diagnostic test that comes onto the EU market after the original registration of the medicinal product remains to be clarified.

Solution:

Development of regulatory guidance is needed to highlight the analytical performance requirements and potential clinical evaluation for "follow-on" companion diagnostic tests that come onto the market after the original registration of the medicinal product.

In-house tests – devices manufactured and used only within health institutions established in Europe:

Barrier:

In the EU, companion diagnostic testing can be performed using CE-marked IVD tests or in-house tests. Currently, in-house companion diagnostic tests with non-transparent performance data are widely used. Therefore, safety and efficacy of these laboratory-developed tests may be questioned when used in conjunction with a specific medicinal product.

Solutions:

In-house companion diagnostic tests should be held to the same quality standard as commercially developed companion diagnostic tests, specifically when they are used to make identical clinical decisions regarding a medicinal product. Further guidance is required on the subject of standards for validation of in-house companion diagnostic tests.

The widespread use of in-house tests also requires precise instructions and careful quality control, to ensure that all patients receive a reliable result to help guide their treatment. The introduction of an "in-house labelling" requirement to increase transparency about the performance of each of these assays is needed. The labelling should include analytical performance data that will improve the understanding of the test.

Lastly, given that the local implementation of a companion diagnostic in clinical practice is highly variable and very often dependent on in-house tests, the EMA and academic societies should cooperate to define EU-wide quality assurance schemes, with a view to ensure that both commercially-available diagnostics and in-house developed tests retain high quality and reproducibility in clinical practice. This could be realised with the support of pathology professional societies, or National Quality Assurance systems.

Clinical evidence of a biomarker

Barrier:

The utilisation of previously generated scientific and technical information related to the companion diagnostic's development process is currently unclear.

Solutions:

In cases where appropriate clinical relevance for a biomarker has previously been confirmed, it should be sufficient to use retrospective data to establish the analytical and clinical performance of a new companion diagnostic test for this same marker.

This should be feasible if the following requirements are met:

- The generation of high-quality observational data with linked biologic specimens for a biomarker assessment as the basis for other clinical utility assessments
- Facilitating the use of retrospective bridging studies, demonstrating that an already existing diagnostic test could be used for another approved medicinal product.

Large genetic panels

Barrier:

The current regulatory system operates under a "one medicinal product – one companion diagnostic" paradigm. However, genetic biomarkers are typically part of larger genetic panels.

Solution:

The approval of diagnostic platforms on general performance metrics (e.g. next generation sequencing platforms) should be introduced, rather than basing the regulation on individual diagnostic targets. This would facilitate the validation of additional biomarkers as well as multi-market genetic signatures. Furthermore, all stakeholders need to join in the discussions to understand current clinical practice and where the technology is evolving. Based on this understanding, a flexible and dynamic regulatory framework for genetic panels should be discussed to promote future innovation in genetic testing.

3 - Post-authorisation

Barrier:

The approval of future extensions of a medicinal product's use to new indications or patient groups could be delayed by the inefficient coordination of the intended use change of a companion diagnostic with regards to the existing registration.

Solution:

Efficient coordination between the medicinal product and companion diagnostic registration pathways is critical for new product indications to reach patients in a timely manner. Therefore, the link between the independent medicinal product (EMA, CA) and companion diagnostic (NB) registration pathways must be revised to arrive at a better-integrated process for approving changes in the post-authorisation phase.

Part II: A clear and predictable process for the economic/value assessment of and access to personalised medicine

Problem statement

Personalised medicine brings many benefits to society: selection of optimal therapy, reduced "trial-and-error" prescribing, reduced drug-related adverse reactions, improved health outcomes, etc.

However, there are still many uncertainties.

Given these uncertainties, healthcare decision-makers are concerned that personalised medicine will increase the costs of new therapies and diagnostics (primarily in the short-term), as well as force the reorganisation of healthcare systems associated with the introduction of personalised medicine. Furthermore, there is a lack of evidence and clarity regarding the contribution that personalised medicines can provide for the sustainability and efficiency of the healthcare system.

The EBE-EFPIA Personalised Medicine Working Group has just launched a project aiming to demonstrate that personalised medicine not only brings improvements in clinical outcomes, but also increases the efficiency of healthcare systems in the long term. With this project, the EBE-EFPIA Personalised Medicine Working Group wants to contribute to improving patients' access to personalised medicine.

Objectives of the project

- The project will provide an **evidence-based analysis** to characterise and measure the benefit of personalised medicine to patients, society and healthcare systems.

- The project will define the benefits of personalised medicine, when compared to non-personalised medical treatments, in terms of health outcomes for patients, productivity gains for society and reduced resource utilisation for healthcare systems. **This evidence-based analysis aims to demonstrate that personalised medicine enhances the long-term efficiency** of healthcare systems (utilisation of services, nursing care, administrative burden, medical practice time, etc.) and broadly benefits society at large (productivity gains).

- The project will make **strategic recommendations** to incentivise the development and adoption of personalised medicine in Europe by decision-makers, thus facilitating the access for patients to innovation.

There are specific questions to be addressed:

1. How can personalised medicine improve the efficiency of healthcare systems? The project

will identify which specific benefits would have the highest impact. For example:

- Better screening and faster treatment selection for a patient
- Reduction and prevention of side effects
- Improved prevention and earlier intervention
- Improved decision making for physicians
- Improved healthcare system capacity

2. What are the main barriers from an economic/access perspective that impede the development of personalised medicine in Europe and what are the best strategies to overcome them?

3. What should be the specific contribution from industry to improve access to personalised medicine and, thus, contribute to more efficient healthcare systems?

The report will be written by Charles River Associates, an independent external consultant and become a reference for further initiatives to develop personalised medicine in Europe.

Part III: A European regulatory framework that is supportive of innovation – creating a flexible and "forward-looking" regulatory and reimbursement environment

The current regulatory and reimbursement systems that are in place were designed for medicinal products that are used in non-stratified patient populations. However, in "personalised medicine", a medicinal product is authorised for use in conjunction with a diagnostic test that allows the identification of likely responders to a medicinal product, thus stratifying the population for which a medicinal product is authorised. This brings opportunities for better patient care, but is also challenging when regulatory and reimbursement decisions need to take into account the evolving science linked to how the product is used or how it should be tested.

1 - The use of multi-marker signatures

Barriers:

- Current regulatory and reimbursement systems are not designed to assess multi-marker signatures, which can evolve over time and may help determine the use of multiple medicinal products.
- Diagnostics and multi-marker signatures developed by academic groups are not subject to regulatory reviews, and quality as well as validity are not often assessed formally.
- Patients, healthcare professionals and health systems are not currently well equipped to understand and explain the use, benefits and limitations of "omics" data in medicine.

The current regulatory environment is designed for a "one medicinal product – one test" paradigm. Biomarker development in many therapeutic areas is already moving in the direction of tests that are composed of multiple markers (often referred to as signatures) identified from multiple data sets from different platforms (genomic, proteomic, pharmaco-genomic, etc.), which are then combined using complex bio-informatics approaches.

Such signatures may inform an entire treatment pathway (i.e. a combination or sequence of treatments), not just one medicinal product. Furthermore, such signatures may evolve over time as more data is collected and analysed. These unique, new features will impact the making of regulatory assessments, in which the use and effectiveness of several therapies are linked to complex signatures. Keeping these indications up to date will be challenging in the current regulatory framework.

This challenge of signal evolution is analogous to the concept of "adaptive pathways". This is the idea that the evidence for a therapy and its related diagnostics evolve over time, thus regulatory assessments will also need to evolve over time.

Similarly, as signatures evolve, the definition of the treated patient population will change, as will the population's relevant clinical outcomes. How a therapy is used and its value determined in that particular setting will also need to evolve over time. Tracking this changing value and adjusting its reimbursement appropriately will represent a significant challenge. Thus, adaptive reimbursement mechanisms are an urgent requirement. If a signature (or evolution of a signature) defines a population with improved outcomes, the possibility to adapt reimbursement to reflect the increased value to patient and healthcare system must be available.

Scientists in industry and academia are already developing genetic (and other biomarker) signature approaches, and are testing these in clinical trial settings. As academic researchers often have access to large clinical and genomic research databases, they may develop their own signatures and place them into clinical practice where improvements in outcomes have been identified. There is currently no regulation related to this type of activity, and they become complex in-house developed tests. Careful thought needs to be given to ensure the quality and validity of these tests, as they will be used in direct treatment decisions for patients.

Implementing signature approaches into clinical practice presents challenges to healthcare systems, healthcare professionals and patients. Such approaches will place new demands on existing clinical information systems, and would ideally be introduced using integrated e-health records. Healthcare professionals will require training in these new approaches and systems to be able to use them in their daily practice.

Increasingly, patients are also seeking genomic sequencing directly from commercial organisations to identify their most suitable treatment options (e.g. Foundation Medicine's FoundationOne). When patients receive this type of personal genomic report, medical advice is often sought on the health implications of the information. Education for patients on the subject of "omics", signatures and the impact of this information on their own treatment options will also require new approaches.

Given these likely developments, the current process for the review of medicinal products and related diagnostic tests is unlikely to be fit for purpose in this new environment – it would represent a major change in regulatory philosophy. This evolution is already being considered in discussions and pilot-projects related to the adaptive pathways approach. Methods to repetitively evaluate the benefit-risk balance need to be considered – with a periodic review that reflects the benefit in relation to the risk and size of the population that is impacted.

Professionals, expert societies or clinical guideline committees, which can oversee evolution of signatures and their introduction into clinical practice, also have an important role to play. A process for EU-wide quality assurance systems for non-commercial diagnostics should be established.

Solutions:
- The EMA could convene a workshop on multi-marker signatures, to gather input from stakeholders (patients, academia, industry, regulators) as to what adequate assessment and regulation of these platforms should look like.
- European professional societies and regulators should discuss the potential for validation and quality assessments of signatures developed by academic groups, which are introduced into clinical practice.
- Member States should embark upon efforts to educate patients and healthcare professionals on the use, benefits and limitations of "omics" technologies in medicine.

2 - The use of electronic health record systems that facilitate clinical research, ease the collection and processing of real-world data and improve clinical practice

Barriers:
- A lack of integrated electronic patient health data systems, and defined inter-operability standards.
- Quality and validity of real-world data (RWD) to support regulatory submissions is often questioned by regulators and payers.

With the evolution of e-health records (eHR), healthcare systems are now able to electronically track patient data (diagnosis, treatment and outcomes) in an almost continuous way (RWD). Currently, RWD is considered different from clinical trial data and often deemed of a somewhat lower quality, as it is not subject to the same rigorous quality controls as data emerging from randomised clinical trials (RCT).

However, progress in informatics technology means that these two data approaches (RWD and RCT) are converging. It is possible to have a very high quality, audited eHR system, where data quality approaches that of randomised clinical trials. Thus, it is possible that in the near future there could be a single electronic clinical data source within a health system which would provide the "real-world" (and potentially "real-time") clinical data, but in a comprehensive and high-quality system that would make the data acceptable for regulatory purposes.

This convergence of eHR systems, RWD and RCT data platforms potentially has extremely significant implications for research, regulation and reimbursement. Currently, there is a separate collection of

overlapping data for different purposes (drug development and marketing authorisation, as opposed to reimbursement purposes) which could be substantially reduced because of this convergence. It is possible that new data generated in clinical trials could become part of the patients' eHR. For example, if multi-marker signatures are generated, these data might be captured in the eHR, so they would not need to be regenerated later. This would require significant new investments in expanded technical capabilities (genetic data handling, consent for the use of data, flagging clinical utility, genetic counselling, etc.).

This would allow new approaches to clinical trials (e.g. registry-based randomised clinical trials). Using an eHR, suitable patients could be identified, their consent randomised into appropriate treatment approaches within normal clinical care, and their trial data collected via normal clinical research practices. This could enable more patients to join clinical trials at a lower cost, and would result in quicker answers to clinical questions, thus contributing to better healthcare. The outlined approaches have the potential to be faster, less costly and more flexible – but they require investment in high-quality, validated eHR platforms within healthcare systems.

Such advances in clinical data collection would support adaptive pathways in regulatory approval. Furthermore, the ability to collect clinical data reliably in practice would also allow for both efficacy and safety data to be collected efficiently in support of post-marketing surveillance studies (i.e. pharmacovigilance).

This new approach to the collection of clinical data (RCT and RWD) would have a significant impact on reimbursement systems. The clinical value of medicinal products and diagnostics can be more readily tracked, as data on their utilisation, as well as other health resources and clinical outcomes, can be collected. Accordingly, innovative reimbursement models, such as pricing by indication or payment based on clinical outcomes, can be more easily implemented.

eHR systems can provide accurate and timely clinical information, allowing for the continued assessments of the benefit-risk balance and value of products in multiple, evolving, well-stratified patient populations. Gaining the most benefit from these systems will require the pooling and analysis of data across countries in order to collect enough data for the evaluation of less common sub-groups of patients. Such systems, therefore, need to be interoperable in the EU – this requires common data standards.

Solutions:

- Launch of an EU-wide clinical data project to define minimal standards and ensure inter-operability.
- The EMA should define quality standards for using electronic data from e-health records in post-marketing commitments (e. g. registry databases) and submissions of applications for marketing-authorisation.

3 - Data protection legislation that effectively facilitates the use of "big data" in healthcare research

Barriers:

- Regulations governing data privacy and informed consent have unintended, highly negative consequences for the use of electronic health records and "omic" data in clinical practice, clinical research, drug development and reimbursement.

The approach to "big data" in healthcare that is outlined in the previous section has large implications for patient consent and data privacy, and will require substantial educational efforts and discussions with stakeholders on the benefits, implications and limitations of such approaches to healthcare.

The European data protection and data consent frameworks must take into account the need to re-use and pool health data in order to allow its analysis for research, clinical care and reimbursement. This needs to occur on a European level to make the best use of these rich data sources, particularly as the application of personalised medicine defines smaller subgroups of patients using precisely identified diagnostic parameters. This has to be balanced with the need for data security, confidentiality and the individual's right to decide on the use of their data.

True anonymity is no longer a viable concept in the face of genomics and detailed clinical data, which implicitly identify an individual. Therefore, there is an urgent need to ensure data privacy and security measures that are appropriate for the genomic age. Educational initiatives and discussions with patients on the potential benefits, implications and limitations of these approaches for healthcare, and progress in health research, will be essential to move these types of initiatives forward.

Current requirements for informed consent lack flexibility and may restrict the re-use of data for further research. More consistent and flexible approaches should be sought. Furthermore, the concept of the "donation" of data to research should also be explored, with the goal to reduce the impact that withdrawn consent (or seeking consent from the family of deceased patients) has on current and future research projects. Dynamic consent platforms could serve a role and other forms of improved accountability to the providers of data should be considered, in cooperation with patients.

Given the need for healthcare systems, regulators, reimbursement agencies and payers as well as academia and industry to access such data, clear agreements are necessary regarding the acceptable use of data.

Finally, the complexity and interdependency of different data sources to provide personalised, data-driven healthcare requires improved collaboration between patients, academia, healthcare providers, regulators, payers and industry – all focused on solving the highlighted challenges.

Solutions:

- The European Commission should enter into a dialogue with all stakeholders about data privacy and informed consent issues to facilitate the use of electronic clinical records and "omics" data in healthcare and research, while balancing the rights and freedoms of the individual.

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Glossary

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Accelerated assessment: from IMI ADAPT SMART glossary
Rapid assessment of medicines in the centralised procedure that are of major interest for public health, especially ones that are therapeutic innovations.

Adaptive pathways: from IMI ADAPT SMART glossary
A prospective planned approach of development, involving all stakeholders to support patient access to medicinal products, that answers an unmet medical need. It foresees initial marketing authorisation and reimbursement of a medicinal product in a well-defined patient subgroup and subsequent widening of the indication to a larger patient population. This is based on additional evidence gathered and/or conditional marketing authorisation and conditional reimbursement where initial data are confirmed through the collection of post-authorisation data on the medicinal product's use.

Analytical performance: from *in vitro* diagnostic medical devices Regulation 2017/746
Analytical performance means the ability of a device to correctly detect or measure a particular analyte.

Analytical validation: from US national library of medicine
Analytical validity refers to how well the test predicts the presence or absence of a particular gene or genetic change. In other words, can the test accurately detect whether a specific genetic variant is present or absent?

Assay: from Wikipedia
An assay is an investigative (analytic) procedure in laboratory medicine, pharmacology, environmental biology and molecular biology for qualitatively assessing or quantitatively measuring the presence, amount or functional activity of a target entity (the analyte). The analyte can be a drug, biochemical substance or cell in an organism or organic sample.

Benefit-risk balance: from IMI ADAPT SMART glossary
Benefit-risk balance is an evaluation of the positive therapeutic effects of the medicinal product in relation to the risks.

"Big data": from IMI ADAPT SMART glossary
Big data represents diverse datasets, the size of which is beyond traditional evidence datasets. The size of the datasets is beyond the ability of typical database software tools to capture, store, manage

and analyse.
Please note: This definition is intentionally subjective and incorporates a moving definition of how big a dataset needs to be in order to be considered big data.

Bio-informatics: from Wikipedia
Bio-informatics is an interdisciplinary field that develops methods and software tools for understanding biological data. As an interdisciplinary field of science, bioinformatics combines computer science, statistics, mathematics and engineering to analyse and interpret biological data.

Biomarker: from IMI ADAPT SMART glossary. Linked to "**multi-marker signature**" or tests composed of multiple biomarkers that are often referred to as signature.
A biomarker is a substance, structure or process that can be measured in the body or by its products and influence, or predict the incidence of outcome or disease.

Bridging studies: from IMI GetReal glossary
A study, supplemental to a randomised controlled clinical trial, designed to provide additional clinical data on the safety, efficacy, dose and regimen. Thus, allowing for the extrapolation of external trial data to a new subject population with (possibly) different population characteristics. An ethnicity bridging study is one example of such a supplemental study.

CE marking test: from *in vitro* diagnostic medical devices Regulation 2017/746
"CE marking of conformity" or "CE marking" means a marking by which a manufacturer indicates that a device is in conformity with the applicable requirements set out in this Regulation and other applicable Union harmonisation legislation providing for its affixing.

Clinical benefit: from *in vitro* diagnostic medical devices Regulation 2017/746
Clinical benefit means the positive impact of a device related to its function, such as that of screening, monitoring, diagnosis or aid to diagnosis of patients, or a positive impact on patient management or public health.

Clinical efficacy: from the European Medicines Agency glossary
Clinical efficacy is the measurement of a medicine's desired effect under ideal conditions, such as in a clinical trial.

Clinical evidence: from *in vitro* diagnostic medical devices Regulation 2017/746
Clinical evidence means clinical data and performance evaluation results, pertaining to a device of a sufficient amount and quality to allow a qualified assessment of whether the device is safe and achieves the intended clinical benefit(s) when used as intended by the manufacturer.

Clinical outcome or clinical endpoint: from IMI GetReal glossary
It is an aspect of a subject's clinical or health status that is measured to assess the benefit or harm of an intervention. A clinical endpoint describes a valid measure of clinical benefit due to intervention – the impact of the intervention on how a subject feels, functions and survives. It is clinically relevant, sensitive (responsive to change) and both accepted and used by physicians and patients. Clinical endpoints may be a clinical event (e.g. mortality), composite of several events, measure of clinical status (e.g. blood pressure) or health-related quality of life.

Clinical performance: from *in vitro* diagnostic medical devices Regulation 2017/746
Clinical performance means the ability of a device to yield results that are correlated with a particular clinical condition, or physiological or pathological process or state, in accordance with the target population and intended user.

Clinical safety: from International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)
The safety evaluation during clinical drug development is expected to characterise and quantify the safety profile of a drug over a reasonable duration of time, consistent with the intended long-term use of the drug.

Clinical trial: from IMI ADAPT SMART glossary
A clinical trial is a clinical study which fulfills any of the following conditions; (a) the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned; (b) the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study; or (c) diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects.

Clinical utility: from the British In Vitro Diagnostics Association
Clinical utility is the demonstration of the potential usefulness and added value of the test to patient management decision-making.

Clinical validity: from the British In Vitro Diagnostics Association
The clinical validity is the demonstration of the performance characteristics supporting the intended use of the in vitro diagnostic medical devices and includes diagnostic sensitivity, diagnostic specificity based on the true disease status of the patient and negative and positive predictive values based on the prevalence of the disease.

Companion diagnostic: from *in vitro* diagnostic medical devices Regulation 2017/746
Companion diagnostic means a device which is essential for the safe and effective use of a corresponding medicinal product to:
(a) Identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or
(b) Identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product.

Compassionate use: from IMI ADAPT SMART glossary
Making a medicinal product available for compassionate reasons to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorised medicinal product (the medicinal product concerned must either be subject of an application for a central marketing authorisation or must be undergoing clinical trials).

Conditional marketing authorisation: from IMI GetReal glossary
A one-year marketing authorisation within the European Union with annual review by the European Medicines Agency (EMA), and which applies in specific cases, such as: (a) seriously debilitating or

life-threatening diseases; (b) emergency threats determined by the WHO, or the EU Commission; or (c) orphan medicinal products. Accelerated drug approval is the near equivalent of conditional marketing authorisation in the USA.

Data privacy: from Wikipedia
Data privacy is the relationship between the collection and dissemination of data, technology, the public expectation of privacy and the legal and political issues surrounding them.

Diagnostic platform: see molecular diagnostics.

Diagnostic test: from Wikipedia
A diagnostic test is a procedure performed to confirm or determine the presence of disease in an individual suspected of having the disease, usually following the report of symptoms or based on the results of other medical tests.

Electronic health record or e-health record or eHR: from IMI GetReal glossary
An electronic record of health-related information on an individual that can be created, gathered, managed and consulted by authorised clinicians and staff within one healthcare organisation. Patient health-related information may include all key administrative clinical data relevant to that person's care under a particular provider, including demographics, progress notes, problems, medications, vital signs, past medical history, immunisations, laboratory data and radiology reports.

"Follow-on" companion diagnostic: from US Food and Drug Administration website
A follow-on companion diagnostic device is defined as having the same therapeutic indication as a FDA-approved companion diagnostic device.

Genomics: from Wikipedia
Genomics is the branch of molecular biology concerned with the structure, function, evolution and mapping of genomes.

Genomic sequencing: from Genome News Network
Genomic sequencing is figuring out the order of DNA nucleotides, or bases, in a genome – the order of As, Cs, Gs and Ts that make up an organism's DNA.

Health Technology Assessment (HTA): from IMI GetReal glossary
HTA is the systematic evaluation of the properties and effects of a health technology, addressing the direct intended effects of this technology, as well as its indirect unintended consequences, and aimed mainly at informing decision-making regarding health technologies.

Indication: from IMI ADAPT SMART glossary
A clinical symptom, disease, risk factor or circumstance for which the use of a particular intervention would be appropriate, as recommended in a clinical practice guideline or protocol of care or by a regulatory body or other authoritative source.

Informed consent: from *in vitro* diagnostic medical devices Regulation 2017/746
Informed consent means a subject's free and voluntary expression of his or her willingness to participate in a particular performance study, after having been informed of all aspects of the

performance study that are relevant to the subject's decision to participate or, in the case of minors and of incapacitated subjects, an authorisation or agreement from their legally-designated representative to include them in the performance study.

"In-house" testing: from *in vitro* diagnostic medical devices Regulation 2017/746
Devices manufactured and used only within health institutions established in the European Union.

International Non-proprietary Name (INN): from the European Medicines Agency glossary
INN is the globally recognised name used to identify the active ingredient in a medicine.

In-vitro diagnostic medical device: from *in vitro* diagnostic medical devices Regulation 2017/746
In vitro diagnostic medical device means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information on one or more of the following:
(a) Concerning a physiological or pathological process or state;
(b) Concerning congenital physical or mental impairments;
(c) Concerning the predisposition to a medical condition or a disease;
(d) To determine the safety and compatibility with potential recipients;
(e) To predict treatment response or reactions;
(f) To define or monitor therapeutic measures.
Specimen receptacles shall also be deemed to be in vitro diagnostic medical devices.

Label: from *in vitro* diagnostic medical devices Regulation 2017/746
Label means the written, printed or graphic information appearing either on the device itself, or on the packaging of each unit or on the packaging of multiple devices.

Laboratory-developed test (LDT): from US Food and Drug Administration website
A laboratory-developed test is a type of in vitro diagnostic test that is designed, manufactured and used within a single laboratory.

Large genetic panels (multi gene panel testing): from National Cancer Institute website
Genetic tests that use next-generation sequencing to test multiple genes simultaneously.

Marketing authorisation (MA): from IMI ADAPT SMART glossary
A MA is a license given by a regulatory authority to an applicant allowing for the marketing of a specific product within the jurisdiction of the regulatory agency. The decision for granting a marketing authorisation is based primarily on the quality, safety and efficacy of the new medicinal product. Additionally, it is based on the evidence of a positive benefit-risk ratio at the time of approval (i.e. the expected benefits outweigh the anticipated risks in a defined population) at a defined dosing and dose regimen, with defined conditions of use.

Molecular diagnostics: from Wikipedia
Molecular diagnostics is a collection of techniques used to analyse biological markers in the genome and proteome—the individual's genetic code and how their cells express their genes as proteins—by applying molecular biology to medical testing. The technique is used to diagnose and monitor

disease, detect risk and decide which therapies will work best for individual patients.

Multi-marker signature: see biomarker.

Notified body: from *in vitro* diagnostic medical devices Regulation 2017/746
Notified body means a conformity assessment body designated in accordance with the Regulation 2017/746.

Observational data: from IMI GetReal glossary
Data collected from populations as present in the routine setting of healthcare (i.e. outside the setting of a randomised controlled trial). Sources of observational data may include routine clinical practice, patient registries, hospital claims databases/administrative data, health surveys, electronic health records, medical chart reviews and post-marketing safety studies.

"Omics": from Wikipedia
The English-language neologism omics informally refers to a field of study in biology ending in -omics, such as genomics, proteomics or metabolomics. The related suffix -ome is used to address the objects of study of such fields, such as the genome, proteome or metabolome respectively. Omics aims at the collective characterisation and quantification of pools of biological molecules that translate into the structure, function and dynamics of an organism or organisms.

Patient access: from IMI ADAPT SMART glossary
The degree to which a patient or group is able to obtain care or services, taking into account the health system's financial and organisational constraints.

Performance evaluation: from *in vitro* diagnostic medical devices Regulation 2017/746
Performance evaluation means an assessment and analysis of data to establish or verify the scientific validity, the analytical and, where applicable, the clinical performance of a device.

Performance study: from *in vitro* diagnostic medical devices Regulation 2017/746
Performance study means a study undertaken to establish or confirm the analytical or clinical performance of a device.

Personalised medicine: from European Council conclusions on personalised medicine for patients (2015/C 421/03)
Medical model using characterisation of individuals' phenotypes and genotypes, or tailoring the right therapeutic strategy for the right person at the right time, and to determine the predisposition to disease and/or deliver timely and targeted prevention, and it relates to the broader concept of patient-centered care, which takes into account that, in general, healthcare systems need to better respond to patient needs.

Pharmacovigilance: from the European Medicines Agency website
Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem. The European Medicines Agency (EMA) coordinates the European Union (EU) pharmacovigilance system and operates services and processes to support pharmacovigilance in the EU.

Post-authorisation: from IMI ADAPT SMART glossary
The period that commences immediately after marketing authorisation of a medicinal product is granted.

PRIME – PRIority MEdicines: from the European Medicines Agency website
PRIME is a scheme launched by the European Medicines Agency (EMA) to enhance support for the development of medicines that target an unmet medical need. This voluntary scheme is based on enhanced interaction and early dialogue with developers of promising medicines, to optimise development plans and speed up evaluation so that these medicines can reach patients earlier.

Proteomics: from Wikipedia
Proteomics is the large-scale study of proteins.

Randomised controlled trial (or randomised control trial, RCT): from Wikipedia
RCT is a type of medical experiment which aims to reduce bias when testing a new treatment. Patients participating in the trial are randomly allocated to either the group receiving the treatment under investigation or a group receiving standard or placebo treatment as the control. Randomisation minimises selection bias and the different comparison groups allow the researchers to determine any effects (including side effects) of the treatment when compared with the no-treatment (control) group. The RCT is often considered the gold standard for a clinical trial.

Registry-based randomised clinical trials: from US National Library of Medicine
Registry-based randomised controlled trials are defined as pragmatic trials that use registries as a platform for case records, data collection, randomisation and follow-up.

Real-world data (RWD): from IMI GetReal glossary
An umbrella term for data regarding the effects of health interventions (e.g. safety, effectiveness, resource use, etc.) that are not collected in the context of highly-controlled, randomised clinical trials. Instead, RWD can either be primary research data collected in a manner which reflects how interventions would be used in routine clinical practice or secondary research data derived from routinely collected data. Data collected include, but are not limited to, clinical and economic outcomes, patient-reported outcomes and health-related quality of life. RWD can be obtained from many sources, including patient registries, electronic medical records and claims databases.

Real-world evidence (RWE): from IMI GetReal glossary
Real-world evidence is the evidence derived from the analysis and/or synthesis of real-world data (RWD).

Scientific advice: from IMI GetReal glossary
Advice given by a regulatory/reimbursement authority to a manufacturer on appropriate tests and studies to be performed during product development/application for product reimbursement, to avoid major objections being raised during the evaluation of the marketing authorisation application/reimbursement application.

Stratified population: from IMI ADAPT SMART glossary
Grouping of patients/subjects by a characteristic (e.g. biomarker, geographic location or age)

Suitability: term extracted from *in vitro* diagnostic medical devices Regulation 2017/746 "Suitability of the device in relation to the medicinal product concerned".
The term is expected to be defined by the EMA following the publication for comment of the EMA "concept paper on predictive biomarker-based assay development in the context of drug development and lifecycle" on 28 July 2017.