
Can digital technology really help to measure meaningful endpoints in clinical trials?

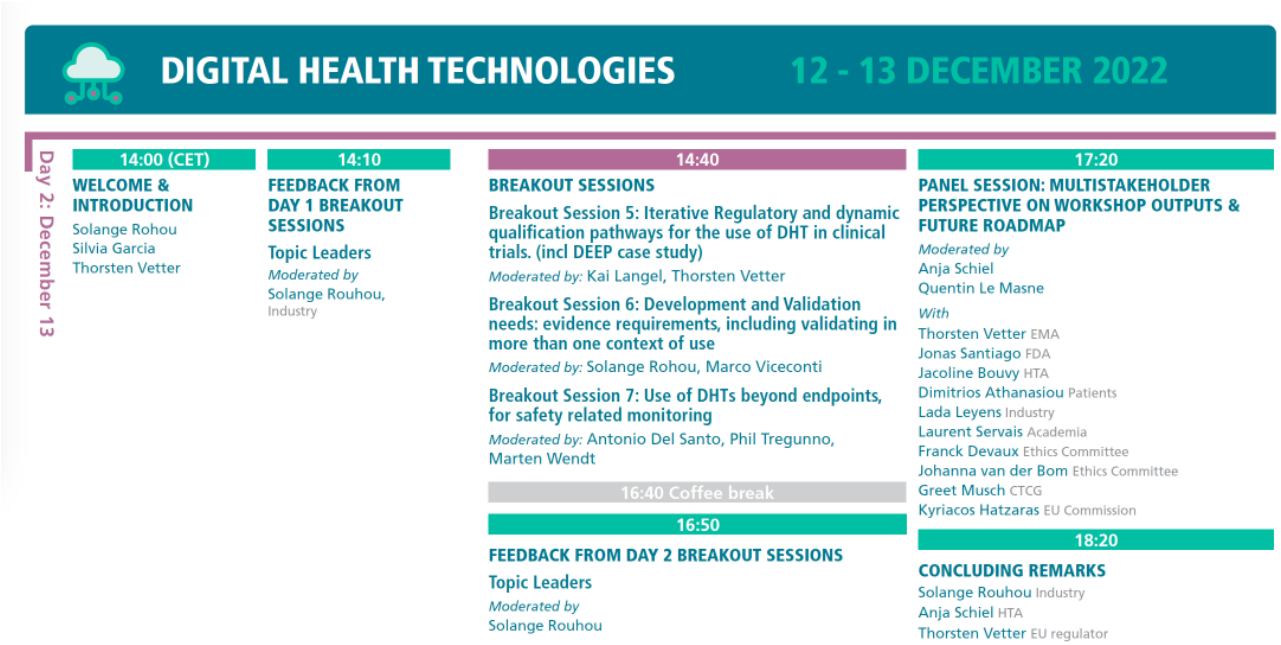
With the right conditions, it certainly can, concluded - with a resounding 'yes' - a December 2022 workshop of international stakeholders in clinical research.

The workshop registered wide agreement on the promise of the rapidly increasing range of new digital health technology (DHT) that can ensure patients are fully at the centre of clinical trials. The participants, from the worlds of research, regulation, health technology assessment, patient organisations, industry and ethics committees, concurred that when these tools are adequately validated and used, they can produce more precise, relevant and sensitive measures to identify treatment effects sooner, in trials that are smaller, even allowing patients to take part in their own home. There was a perceptible sense of momentum for the future deriving from the last two decades of digitalization of clinical research. “We are all convinced that this is the right way to go to obtain patient-relevant data. The question is not if but when," as one participant in the workshop summed it up.

There are still many challenges to be overcome. Agreement must be found on validation methods for these tools, and on guarantees of rigour and quality when including measurements of endpoints and outcomes from DHTs in clinical trials. Patients and their physicians need to be more fully engaged in the design and development of DHTs and their deployment. The use of novel techniques must be justified in terms of added value compared to existing available measures. Developers need to be confident of the business case for the investments required, particularly for securing regulatory and reimbursement approval in a highly divergent environment. There is still significant variation among regulators and HTA bodies in Europe in their attitudes and responses to digital health (DH), and the context for innovation would be more encouraging with a greater degree of alignment across them. At the same time, skills need to be developed across the board to respond to new ways of approaching clinical trials.

Breakout sessions examined many of these challenges in detail, and some of the workshop recommendations are set out briefly in this report. But this was acknowledged to be only a step along the road, and the chief sentiment to emerge from the workshop, alongside a sense of optimism, was a unanimous determination to collaborate more closely in turning the promise into a reality.

The digital health technologies virtual workshop on 12-13 December 2022 heard reports from ethics committees, officials and regulators from the EU, the member states and the US on their experiences, and priorities and expectations were set out by patients, academia, non-profit investigators, developers, and health technology bodies. Breakout sessions explored data and measurement standards, patient engagement, prognosis and diagnosis, qualification pathways and evidence requirements for validation, and safety-related monitoring. And a multistakeholder perspective and the shape of a future roadmap was forged on the basis of the workshop outputs.

**The promise**

DHT is providing new data-generation tools that can continuously deliver more precise, relevant and sensitive monitoring and measurements, maximising data from fewer patients. If the challenges for validation/qualification are satisfactorily met, this access can accelerate trials and increase the probability of trial success, making the best use of cost and time. Novel patient-centric outcome measurements can facilitate patient convenience and inclusivity, and enhance patient access and experience. Innovative approaches can reduce dropouts of patients from trials and better detect meaningful changes, as well as improving the quality of application dossiers and the chance of regulatory approval.

Digitalization of clinical research is moving firmly from theory to practice, and digital technology is expected to account for 80% of data collection in clinical trials by 2025, as expressed by a speaker during the workshop. Hesitation over its potential is giving way to increasing recognition and growing deployment, as advances with mobile apps or wearables with miniaturised biosensors are used on a daily basis, not only to improve the reporting but also to transform monitoring from reactive into more proactive approach. European Medicines Agency (EMA) participants say they see benefits in decreasing missing data, increasing observation of patient functioning in a real-world setting, streamlining clinical investigations and delivering remote data capture and patient monitoring. They see an opportunity for assessment of therapeutic needs that in the light of digitally derived data reflects more precisely how patients feel and function and survive and flourish.

The need to exploit new possibilities is more urgent than ever. At present, particularly for patients with rare diseases, the number of trials is strictly limited by the challenges in patient recruitment, and those that do take place suffer a distressingly high level of failure, leaving many people without effective therapy. DHTs have a role to play in significantly improving the focus of research and the sensitivity in capturing endpoints that matter to patients - and they hold out the hope for increasing the success rate of development.

## The conditions

The promise will not be realised automatically. There are conditions to be met and challenges to be overcome – not least in validation/qualification, management of measurement artefacts, minimal clinically important differences, and the ability to detect clinically patient relevant change. In consequence, the potential is still sub-optimally exploited, and advanced DHT is still underused in clinical trials.

Evidence

There must be agreement on the level of evidence and the degree of rigour and precision when validating DHTs and using their measurements of endpoints and outcomes in clinical trials. This means that DHTs must be verified as fit for purpose, and the clinical investigation endpoints must target an outcome of interest. Developers' experience with these qualification procedures is however still limited.

Regulators are also learning how to approach the review of data collected via DHTs in clinical trials for benefit/risk evaluations. From a regulatory perspective, it is important to differentiate between the DHT that collects the data, and the digital measure or parameter that is used to infer treatment benefit. In both the United States and Europe, DHTs intended only for use in clinical investigations to measure drug treatment effect may be exempt from requirements of medical device premarket approval if their intended purpose does not fit the medical device definition[1]. When it comes to qualification, only the digital measure is qualified by EMA and Food and Drug Administration (FDA), and not the DHT. For the Agencies it is important that the DHT collects data according to ALCOA+ principles[2] and that the data is reliable to inform regulatory decision making. Also important to note is that a CE mark[3] or US device clearance for a DHT does not necessarily mean that it is considered appropriate for use in a particular clinical investigation or that the data collected is reliable for regulatory / health technology assessment (HTA) decision making. Voluntary regulatory pathways of qualification for novel methodologies are available both from EMA and FDA, and existing guidelines are under further development.

The underlying question from regulators and more specifically from HTA bodies will in any case be "*what do these tools bring in terms of added value compared to existing available measures and how do we balance the opportunities they bring to broaden options for patient participations while preserving the regulatory confidence of DHT clinical trial quality and integrity?"* Any novel method should be superior to existing methods in gathering information, sufficient to justify the approach from the point of view of the patient and the regulator, in a way that is consistent across individuals and subgroups, they have made clear. Mere invocation of the potential will not be considered sufficient: developers should be ready to bring regulators an early and well-defined idea about their evidence generation plans for qualification of the digital measure.

---

[1] Regulation (EU) 2017/ 745 of the European Parliament and of the Council - of 5 April 2017 - on medical devices. 5.5.2017 EN Official Journal of the European Union L 117/1

[2] Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring, Available

[3] CE marking shows that the manufacturer has checked that a product meets EU safety, health or environmental requirements.

Patients

Patient engagement has to be more than a mere verbal commitment. It requires ensuring that the patient aspect is central at all times, respecting trial participants' preference for as few DHTs as possible to capture multiple endpoints and ensure optimal usage of data. The tools for the conduct of trials have to be conceived and created with the patient in mind, so that they are easy for the patient to use and ultimately contribute to patient well-being. Patient preferences need to be taken into account even in the early design – and subsequent evolution - of devices so that they are not so obtrusive that the patient is unhappy. Patient feedback is a key test of whether a particular approach is effective. According to a 2020 Association of Clinical Research Organization (ACRO) report, more than 50% of potential trial participants reside more than 2 hours from the trial site, which can severely limit participation. DHTs have a role in further enabling decentralized trials (DCTs) to encourage participation of non-traditional and underserved patient populations where greater attention is required to ensure that the patient benefits of easing travel schedules and costs or improved quality of life do not come at the cost of impersonalising the process and denying a real-world voice to patients.

Business case

Developers intending to use DHT for the endpoints struggle with deciding whether they should first qualify the measures collected by the DHT (e.g. as a Drug Development Tool in the US or novel methodology in Europe) or directly have discussions with regulators on their particular trial. Development teams are often challenged in determining when to qualify a DDT and how such a qualification of a new tool would appear in the eyes of regulatory authorities when preparing a clear business case for the DHT. Obtaining qualification for an outcome measure is further complicated by more complex financial questions for DHT development compared to traditional medical product development, where a higher return on investment early may be expected to justify such investment. This calculation is further complicated by the question on the acceptance by HTAs and whether a regulatory qualification of a novel measure will result in acceptance by HTA bodies. It needs to be acknowledged that the question addressed by both health authorities (HA) and HTA during their review is different; however, this results in a degree of uncertainty and fragmentation in decision-making that many stakeholders see as a persistent obstacle to effective innovation, particularly since development projects tend increasingly to be global.

HTA

HTA participants at the workshop also stressed the difference between their priorities in assessment and those of the regulatory process. They underlined their preoccupations with how a technology compares with the standard of care, with the impacts on the patient of the demonstrated endpoints, and with what it costs over a long-term perspective. They want to see an established association between the digital endpoint and the patient's health-related quality of life and/or survival. The business case therefore has to also take account of the challenges of obtaining national reimbursement – a process that is often subject to lengthy delays, and that was described by some participants as "*intimidating*". It is widely recognised that HTA bodies are not always enthusiastic about ventures into new terrain, and the workshop heard candid admissions from the HTA community of their innate conservatism and risk aversion.

Regulatory frameworks

Due to the lack of globally harmonized terminologies and regulatory requirements applicable for drug-development pathways and device development, it is challenging to engage with the regulatory bodies for drugs and devices in parallel that sometimes delays innovation.

The qualification and assessment frameworks are seen as complex, lengthy and needing more collaboration both within industry and among regulators, as well as with HTA bodies. Challenges include a lack of alignment on terminology, of standardisation and harmonisation of measurements and methodologies across endpoints and disease areas, and limited availability of information on distinct regulatory approaches. Early discussions among global regulatory bodies and relevant stakeholders for a harmonized approach to using DHTs across medical product development is critical to avoid siloed or niche DHT regulatory frameworks being developed in specific localities. At the same time skills need to be developed in regulatory agencies to respond to the assessment of future marketing authorization applications that contain the use of novel methodologies and technologies as part of drug development, such as for example data generated by using artificial intelligence.

Collaboration

Collaboration in DHT-derived endpoint development and data sharing raise their own challenges because of the constraints resulting from privacy issues and the questions arising from proprietary information and intellectual property. Making more information available, even with some mandatory elements, could be advantageous in some circumstances to achieve global harmonisation and enable a learning ecosystem but runs repeatedly into the limits of privacy. Regulators and industry are discussing how much information should be disclosed within qualification procedures with the public to support these goals. However, challenges of potential sharing of confidential data need to be considered and addressed.

## The prospects

Participants at the workshop drew comfort from the following wind that appears to be blowing increasingly strongly in favour of DHTs.

Results are expected in early 2023 from a comprehensive industry survey of expectations and acceptance, but already it is clear that most leading biopharma companies have experience with implementing digital endpoints at least in exploratory endpoints, and are now moving significantly into secondary and primary endpoints.

Further to the workshop and as announced, a recommendation paper[4] on decentralised elements in clinical trials in the EU was published in December 2022, focusing on a participant-centred and risk-based approach to trials, with investigator and sponsor oversight to generate reliable and robust data fit for purpose. It also carries a helpful – if ominous – list of the distinct national provisions currently non-aligned with EU recommendations.

Encouraging sounds came from some HTA participants, who expressed interest in seeing what might be done differently, and even urged that they may have more in common with regulators than received opinion suggests. Some of them spoke of seeing whether there is not more that can be done to support industry and tech companies who are operating in this new space, without lowering standards. There was recognition that early involvement in developments – among technology companies, regulators, HTA bodies and patients could help to avoid much of the fragmentation that can currently impede development. The forthcoming implementation of the EU HTA regulation[5] in 2025 could well provide an opportunity for further engagement and collaboration among HTA bodies and with stakeholders, it was suggested.

Some participants reported that they had already encountered increased understanding among regulators of the potential of digitally derived outcomes. This has given rise to hopes that evolution in the field could even allow new DHT applications to benefit from wider experience of interaction with regulators, to increase regulatory experience and confidence in the use of novel technologies and avoid or circumvent some of the current regulatory hesitancy. Valuable joint work has been carried out through public private partnerships such as IMI, and the European Commission and regulators are involved in global initiatives to improve the efficiency of clinical trials. EFPIA has declared its commitment to supporting the development of a multi-stakeholder platform that would enable further discussion across the rapidly evolving clinical trial landscape. And an EMA workshop on the qualification of novel methodologies which is planned for April 2023 will have a dedicated session on the qualification of DHTs.

Above all, there is a growing recognition that there is more to DHTs than was originally realised in monitoring devices for glucose for management of diabetes, or in using them to identify endpoints for clinical trials. DHTs also have a potential role in improving the

[4] https://health.ec.europa.eu/system/files/2022-12/mp_decentralised-elements_clinical-trials_rec_en.pdf
[5] https://ec.europa.eu/commission/presscorner/detail/en/IP_21_6771

inclusion of the right patients, protecting patient safety and predicting adverse events, defining better outcomes, and permitting extrapolation, particularly of learnings from large indications to smaller indications. “The potential is definitely there but we do need clarity from a regulatory viewpoint,” insisted participants.

## The recommendations

The recommendations highlighted below are illustrative. The process is ongoing, and a fuller paper is expected to emerge from the discussions that took place at the workshop. But key points that emerged include:

- Success will depend upon wider and closer collaboration in addressing the challenging issues, and many participants expressed satisfaction at hearing examples of where collaboration might make a significant difference. There was enthusiastic endorsement of maximising structural collaboration in the pre-competitive space with efforts such as the Innovative Health Initiative (IHI), the Critical Path Institute (C-Path), Digital Medicines Society (DiME) and the Digital Evidence Ecosystem and Protocols (DEEP) initiative, and of clear definition of existing gaps to guide the use of these DHTs, along with suggestions that it may be appropriate to focus initially on major clinical areas.

- A constant refrain throughout the workshop was the call for greater regulatory alignment on terminology, definitions, and standards, not only among regulators but among and with HTA bodies and industry, that will encourage more global harmonization among DHT frameworks. Terminology needs clarifying to provide a better basis for understanding.

- Learning from achievements so far should be maximised, with a focus on education and creation of standards on evidence generation for regulatory purposes as well as informing future design of regulatory pathways, based on shared outcomes.

- Qualification procedures need particular attention, and experience should be exploited to help optimise that process, and create seamless pathways that avoid unduly complicate review and acceptance process.

- Other key areas requiring guidance are on the evidence that will be needed for systems supporting data capture and capture and management, especially for sensor based technologies, on the fitness for purpose of each individual system, and on issues such as how to handle critical safety data generated real time by digital health technology. Engagement across a multidisciplinary set of traditionally divided industry stakeholders (drug/biologic vs device development) will be critical when developing such guidance to better clarify the many technicalities and regulatory pathways of DHT use in therapeutic product development. There is also a need for pragmatism in finding the balance

between calls for transparency and working with data that is covered by IP and confidentiality considerations.

- Because of the novelty of many aspects of this field, skills development and training was seen as essential not only among developers, but equally among all other stakeholders ranging from patients and their advocacy organisations to regulators, health technology assessment bodies, and ethics committees. Patient representatives in particular made the case for greater provision for education, not least so that they can contribute more meaningfully to discussions of the procedures in moving ahead with digital endpoints.

## The conclusion

There was a perceptible sense of excitement among participants at the prospects. And amid all the challenges, the workshop reflected a commitment from across the spectrum of stakeholders to work together towards solutions, and to maintain the momentum in the coming months.

Realistically, it is accepted that there is no possibility of finding solutions immediately to all the issues, but follow-up action is planned. There was a welcome for the level of ambition, and appreciation for the opportunity to hear many distinct views from the multiple stakeholders. One participant summed it up: “At the moment everyone is open, everyone is listening and there are very few critical voices. Hardly anyone denies the potential and we're all looking at how we can use it.”

Yes, there are obstacles, but none of the obstacles sound like it's going to block the road ahead. The discussions and proposals identified during the workshop will inform further exchanges, and the work is scheduled to continue.

**Breakout sessions**

Seven breakout sessions explored workshop issues in detail. Breakout session 1 covered the importance of developing data and measurement standards to enable efficient data collection management and analysis. Breakout session concluded from 2 case studies that multi-component measures are valuable to capture a multi-dimensional aspect of health. Breakout session 3 covered patient engagement and the importance of the patient voice. Breakout session 4 covered prognosis, patient selection and diagnosis. Breakout session 5 covered qualification pathways. Breakout session 6 covered evidence requirements for development and validation. And breakout session 7 covered safety related monitoring.

**BOS 1: Data and measurement standards in the use of DHT and digital endpoints in clinical trials**

This session covered the importance of developing data and measurement standards for the use of digital health technologies in clinical trials to enable efficient data collection, management and analysis. When collecting data in clinical trials for regulatory decision making, there is also a need to ensure compliance with GCP, as well as other applicable GxP guidance documents. A white paper is planned that will summarize the results of the discussions and include calls to action.

BOS1 Key outcomes

Major challenges include:

- lack of standardization and harmonization of measurements across disease areas.
- real-time data collection and quality assurance during data collection.
- the proper validation of devices and supplementary data (such as device metadata) associated with DHTs.

The end-to-end clinical data lifecycle will benefit from standardization.

- some existing standards (from Clinical Data Interchange Standards Consortium Study Data Tabulation Model (CDISC SDTM), Clinical Data Acquisition Standards Harmonization (CDASH) and Medical Devices guidelines) can be adopted.
- in addition to the digital endpoint, other key pieces of information need to submitted (why the feature is fit-for-purpose, device information. data management and integrity, data privacy and security….)

The trial participants expect to

- be burdened with as few DHTs as possible to capture multiple endpoints.
- consider optimal usage of data, with no duplication and maximal expected benefits for the patients.
- receive a report of the personal data at the end of trial in a form understandable and relatable to their disease

BOS1 Potential solutions/call for action

- Although the raw data plays an important role, the community will focus first on the standardization of feature data.

- Recommendations from DIS are expected in 2023 on some data standards implementation.
- Guidances on the evidence support documentations are required.
- Tolerance levels of noise and missing data for clinical trials and Real World Data (RWD) need to be reported.
- Existing cross-industrial DHT initiatives need to put different puzzle pieces together.
- Closer pre-competitive collaboration between multiple stakeholders is expected to facilitate this process.

**BOS2: Exploration of two use-cases using multi-component and multi-modal digital measures**

Teams continue to explore different novel approaches for multi-component and multi-modal digital measures (multi-modal measures are defined as combining components such as tasks and actigraphy across modalities), but the analysis methods are still in early development. A review of IDEA FAST[6] and Roche PD Digital Health Technology Platform v2 suggested a continuing need for alignment on terminology and for adequate justification of multiple modalities that introduce a burden to patients. Use of multiple technologies increases the need to incorporate user experience as part of an endpoint development framework.

<u>BOS2 Key outcomes</u>
Multi-component measures can be valuable to capture

- A multi-dimensional meaningful aspect of health or concept of interest
- And/or in conditions with heterogeneous manifestations

Components/features can be selected for inclusion in a multi-component measure based on patient input or analysis of patient sensor data.
A data-driven multi-component measure may be able to deliver meaningfully in its ability to predict disease outcomes, but longitudinal data are needed to understand how the measure aligns with clinical outcomes.

Multi-modal measures

- The need persists for alignment of terminology.
- Using multiple modalities has the potential to introduce burden to patients.
- Necessary to ensure information is worth it, or consider simplifying (e.g., w/a PRO or identifying the most patient-relevant and sensitive components).
- Use of multiple technologies increases the need to incorporate user experience as part of endpoint development framework.

<u>BOS2 Calls for action</u>
Keep patients at the forefront in determining whether "patient-" or "data-centric" patient-input is essential (such as to define a meaningful aspect of health and to understand usability).
Digital endpoints development needs to be a community effort:

[6] Identifying Digital Endpoints to Assess Fatigue, Sleep and Activities of Daily Living in Neurodegenerative Disorders and Immune-mediated Inflammatory Diseases

- Engage with regulators early and collect feedback.
- Collaborate within industry and share lessons learned.
- Collaborate more closely on endpoint and tool development at pre-competitive stage.
- Create awareness on complexity of developing a multi-modal/multi-component measure.
- Invest in the development of methods (e.g. to validate in absence of a gold-standard anchor, feature selection/weighting, application of innovative approaches such as Machine Learning (ML))

**BOS 3: Patient engagement: establishing patient relevance and the importance of the patient voice**

The growing interest in patient involvement in clinical trials is particularly important for a successful program when developing new endpoints or selecting and developing DHTs, to ensure that what is measured is relevant to patients. This session shared experiences and identified recommendations to optimise patient involvement in design and conduct of clinical trials including DHTs, taking account of learnings from the Innovative Medicine Initiative (IMI) Patient Preferences (PREFER) project.

<u>BOS3 Key outcomes</u>
While digital development does not differ fundamentally from other developments, its novelty presents a valuable opportunity to include patients from the start.
The patient voice needs to be involved from concept and throughout the entire life-cycle - even as early as in the development of the tools for researching patient experience evidence.
Developers should ensure the involvement of patients at an early stage of development of the digital measure.
Include patients as part of focus groups or panels to provide input on an ongoing basis, in addition to pooling them via surveys.
The number of patients should be evaluated in light of the disease area and population and informed by statistical models.
Digital health tools might provide a better medical picture of what a patient is experiencing, as DHTs are closer to real world conditions and can provide a more accurate representation.
There is a need to engage with regulators for the qualification of tools, and to discuss the standards they need to fulfil.
Diversity, considering ethnicity, race, gender, age etc, is as essential in development of digital health tools as it is in any development.
Representativeness for target population and avoidance of bias in training datasets needs to be ensured, in particular when AI/ML is involved.

<u>BOS3 Potential solutions/call for action</u>
Include patients in the development of digital health from initiation throughout the life-cycle:
- not only in pharmaceutical but also in device development.
- using focus groups or panels to obtain patient input on an ongoing basis.

- including as many patients and as representative from target patient population as possible.

Develop a framework for the qualification of tools, with a clear role for patients in the process.

**BOS4: Prognosis, patient selection and diagnosis**

BOS4 Summary of key points

Participants acknowledged that DHT offer an unprecedented opportunity to improve healthcare, and can be used in clinical studies to:

- enable remote data collection in decentralized clinical investigation.
- improve access to clinical investigations.
- facilitate innovative clinical investigation of endpoints.
- capture RWD and Patient-Generated Health Data (PGHD).

Not all DHT are classified as medical devices, in line with key principles outlined in the EU Medical Devices Regulation (MDR) (patient risk, intended use).

Enabling reimbursement of digital technologies is as important as approval (e.g. Germany's BfArM involvement in assessment has resulted in the Digitale Gesundheitsanwendung (DiGA) directory, which offers transparency on reimbursability for users, doctors, health insurers).

The use of DHT in clinical studies should aim to limit inequities (e.g. across different disease groups and with different physical and sensory limitations). Although stakeholders acknowledged the great potential of DHTs to address health inequities, they also emphasized the importance of getting innovative technologies such as Artificial Intelligence/Machine Learning (AI/ML), be it through accounting for bias, understanding what would suffice for each regulator, and how such technologies should be carefully considered to not further perpetuate the health inequities/disparities.

DHT are useful in generating objective, longitudinal Real World Evidence (RWE). In parallel to FDA guidance, multiple EU guidance is currently emerging (e.g. EU guidance on Decentralised Clinical Trials (DCT) published end of Dec 2022 with the aim of facilitating the use of digital approaches in the EU).

Additional challenges arise from the fragmented EU regulatory environment with its multiple decision-makers (e.g. National Competent Authorities (NCAs), Notified Bodies (NB), EMA etc). As global regulatory bodies gain more experience with the use of DHTs across therapeutic product development, it will be equally important to create an integrated DHT framework applicable across both drugs/biologics and device development.

BOS4 Potential solutions/call for action

Focus on patient-centric approaches to generate clinically meaningful data that addresses patient needs and promotes health equity.

Encourage expertise-based international collaborative communities to identify solutions ensuring that:

- DHT including Al/ML are accurate, precise, unbiased, representative.
- manufacturers can rapidly Improve software products, ensuring there are no changes to the validity of the measures that inform regulatory decisions with software changes.
- reimbursement is enabled.
- Good Machine Learning Practices (GMLP) for medical devices can be developed.

Continue the dialogue on whether to focus on qualification for the use of novel technologies or employ derived measures, discuss in product-specific scientific advice or submit DHT-derived evidence as part of Marketing Authorisation Applications (MAA) with subsequent due justification/demonstration of validity (with concomitant risks).
Continue collaboration across agencies in the generation and harmonization of guidance.
Consider pre-specified change control plans to outline future changes that do not need formal regulatory approval.
In view of the rapid evolution of technologies (e.g. AI/ML), regulators invite sponsors and technology developers to engage early in formal and informal dialogue on evidentiary requirements for specific DHTs within an intended use.
Beyond the innovation offices that agencies have created to facilitate informal discussions beyond formal scientific advice and qualification procedures (as has been done in Germany and many other national HAs in EU member states) regulators could consider other ways to support innovators.

**BOS 5: Iterative and dynamic regulatory pathways**
This session considered iterative and dynamic regulatory pathways for the use of DHT in clinical trials, taking account of experience to date in measuring digital mobility outcomes. It focused on SV95C in Duchenne Muscular Dystrophy (DMD), the IMI Mobilise-D programme, and the DEEP initiative.

<u>BOS5 Key outcomes</u>
The experiences of IMI Mobilise-D and SV95C in DMD in qualification advice and qualification procedures differed, with one team going directly through opinion, and the other through advice.

- An early iterative process is preferred.
- A return to parallel EMA and FDA procedures (lost with the US 21st Cure Act) – or similar suitable mechanism that facilitates global qualification of measures - is desirable.

Survey results from EFPIA on the use of DHTs in Europe highlighted that:

Sponsors have more experience with Scientific Advice (SA) than with Qualification of Novel Methodologies (QoNM) and that QoNM is not always the pathway selected for discussing novel methodologies.

Key challenges exist internally and at regulatory level (but regulatory can also be an enabler).

Increase transparency and discuss early with regulators:

- Extrapolation comes down to specific measures: dialogue with agencies is essential, focused on each development.
- Context of use is key to determine validation and to determine evidence requirements for qualification.

Current qualification procedures are considered as

- Resource-intensive, lengthy, relatively unknown within industry and therefore subject to uncertainty. More collaboration among industry and applicants as well as between regulators can help solve some of the challenges.
- Subject to challenges over transparency in sharing qualification HA input (which could also be a key enabler). Public disclosure would be new enabling step to foster and facilitate the qualification of innovative methodologies, and this will need industry buy-in and commitment to share information for the common good.
- Visibly benefitting from EMA-FDA commitment to cooperation in improving procedural agility and harmonised decisions in qualification of novel methodologies.

HTA must be considered alongside clinical practice needs, and since evidence needs may be similar for both, both sides should be involved in qualification

<u>BOS5 Key solutions and call for action</u>
Transparency: needed and seen as an enabler

- in increased data sharing (business models and alignment with Intellectual Property (IP) protection needed).
- in sharing key outputs from qualification advices.
- in pre-competitive collaboration – but better ways are needed.
- building on IHI, Critical Path and DiME, new parties in the ecosystem such as DEEP may be able to provide a solution to enable ecosystem-level scaling.
- HTA and clinical practice: big potential in the use of DHTs in clinical trials with real world clinical practice use and a connection to HTA needs.
- in improved agility in regulatory procedures, while retaining high-quality regulatory feedback.
- in iterative qualification procedures between HAs but also for additional context of use and for moving from secondary to primary.
- in further engagement to improve the current fragmented landscape between HAs and NBs in Europe, but also among global health authorities

Key words during the workshop were collaboration, data sharing, transparency, patient voice, clinical validity, analytic validity, reliability, iterative milestones, financial incentives, validation in patients, and relevance.

**BOS 6: Evidence requirements for development and validation**

<u>BOS 6 Key outcomes</u>

- Although many toolkits exist (Clinical Trials Transformation Initiative (CTTi), DiME, TransCelerate), some issues are not yet explored (e.g. missing data, validation in broad context of use…).
- Digital measures should measure an aspect of the disease recognised as important by patients and doctors.
- Technology should be selected that is appropriate for the patient.
- It is important that the digital measure accurately measures the concept of interest and that measurement performance is consistent across individuals and sub-groups.
- The novel measure should be superior to existing methods.

Broad context of use

- If a concept is common and meaningful across diseases, qualification could be appropriate across multiple diseases.
- Technical validation may not need to be repeated in every new context of use.
- Opinions differ over whether an efficacy measure requires demonstration of sensitivity to change in an interventional trial.

Qualification

- Qualification meetings can allow valuable deep scientific discussion about the measure.
- The right expertise must be available.
- Practical issues must be taken into account: Qualification is voluntary, but developers will of course need to make sure that the DHTs to be used in major/pivotal CTs are valid, otherwise data may be found inadequate to support B/R decision making when submitted for MAA; Qualification should indeed facilitate broad application of valid novel methodologies by many medicinal product (MP) developers, but Qualification will be for a specifically defined context of use;

<u>BOS6 Potential solutions/call for action</u>

Build on existing methodology and advance it to tackle issues such as missing data and broadening the context of use.

Collaborate on, and consider qualifying, common validation methodologies across endpoints (such as how to demonstrate clinical meaningfulness/patient relevance).

Develop greater clarity on regulatory and HTA requirements for validation of digital measures. Such as the need expressed by health authorities for generating data to demonstrate sensitivity to change in an interventional trial.

Regulators' expansion of their technical expertise to support scientific advice is a valuable path to pursue.

**BOS 7: Safety-related monitoring**

<u>Key outcomes</u>

Mobile apps and wearables used daily can improve pharmacovigilance reporting (ex. Recognising Adverse Drug Reactions (WEB-RADR Vigilance Hub), post-vaccination follow-up during the COVID pandemic).

Advanced DHT still seems to be underused in clinical trials.

Regulatory concerns over DHT-generated critical safety data need to be addressed.

DHT's potential for detecting clinical deterioration or asymptomatic conditions at an early stage can improve patient safety.

Remote monitoring devices (eg continuous glucose monitoring) can inform medical product development

<u>BOS7 Potential solutions/call for action</u>

Initiatives are needed to set standards for DHT safety surveillance in clinical trials within the major clinical areas (cardiology, diabetes, etc), involving sponsors, investigators, regulators

and patients. Validating DHT for clinical trials is a complex process, access to validated DHT ”off the shelf” would accelerate their use in clinical trials.

Acknowledgements: The digital health technologies virtual workshop on 12-13 December 2022 heard reports from ethics committees, officials and regulators from the EU, the member states and the US on their experiences, and priorities and expectations were set out by patients, academia, non-profit investigators, developers, and health technology bodies. Breakout sessions explored data and measurement standards, patient engagement, prognosis and diagnosis, qualification pathways and evidence requirements for validation, and safety-related monitoring. And a multistakeholder perspective and the shape of a future roadmap was forged on the basis of the workshop outputs. The organisers warmly acknowledge the input not only from speakers, panellists, breakout session leads, and all other participants.

# DIGITAL HEALTH TECHNOLOGIES 12 - 13 DECEMBER 2022

Day 2: December 13

**14:00 (CET)**

**WELCOME & INTRODUCTION**

Solange Rohou
Silvia Garcia
Thorsten Vetter

**14:10**

**FEEDBACK FROM DAY 1 BREAKOUT SESSIONS**

Topic Leaders

*Moderated by*
Solange Rouhou, Industry

**14:40**

**BREAKOUT SESSIONS**

**Breakout Session 5: Iterative Regulatory and dynamic qualification pathways for the use of DHT in clinical trials. (incl DEEP case study)**

*Moderated by:* Kai Langel, Thorsten Vetter

**Breakout Session 6: Development and Validation needs: evidence requirements, including validating in more than one context of use**

*Moderated by:* Solange Rohou, Marco Viceconti

**Breakout Session 7: Use of DHTs beyond endpoints, for safety related monitoring**

*Moderated by:* Antonio Del Santo, Phil Tregunno, Marten Wendt

16:40 Coffee break

**16:50**

**FEEDBACK FROM DAY 2 BREAKOUT SESSIONS**

Topic Leaders

*Moderated by*
Solange Rouhou

**17:20**

**PANEL SESSION: MULTISTAKEHOLDER PERSPECTIVE ON WORKSHOP OUTPUTS & FUTURE ROADMAP**

*Moderated by*
Anja Schiel
Quentin Le Masne

*With*
Thorsten Vetter EMA
Jonas Santiago FDA
Jacoline Bouvy HTA
Dimitrios Athanasiou Patients
Lada Leyens Industry
Laurent Servais Academia
Franck Devaux Ethics Committee
Johanna van der Bom Ethics Committee
Greet Musch CTCG
Kyriacos Hatzaras EU Commission

**18:20**

**CONCLUDING REMARKS**

Solange Rouhou Industry
Anja Schiel HTA
Thorsten Vetter EU regulator

## Scientific and Technical Program Committee

Anja Schiel (Norwegian Medicines Agency, European Medicines Agency)
Cecile Ollivier (Critical-Path Institute)
Dimitrios Athanasiou (Eurordis)
Elke Stahl (Federal Institute for Drugs and Medical Devices - BfArM)
Franck Devaux (Hôpital Universitaire Des Enfants Reine Fabiola - HUDERF, Ethic Committee - Belgium)
Greet Musch (Federal Agency for Medicines and Health Products - AFMPS; Clinical Trial Coordination Group chair)
Jesper Kjaer (Danish Medicines Agency - DKMA)
Thorsten Vetter (European Medicines Agency)
Wan-Fai Ng (Newcastle University - IMI IDEA-FAST)
Alison Bond (Amgen)
Aude Clement (Novartis)
Cathelijne de Gram (Janssen Biologics BV)
Christine Mayer-Nicolai (Merck)
Lada Leyens (F. Hoffmann-La Roche) (co-lead)
Lesley Maloney (F. Hoffmann-La Roche)
Mireille Muller (Novartis)
Quentin Le Masne (Merck)
Solange Corriol-Rohou (AstraZeneca, IMI MOBILISE-D) (co-lead)
Aneta Tyszkiewicz (European Federation Pharmaceutical Industry Associations)
Silvia Garcia (European Federation Pharmaceutical Industry Associations)

## Speakers, panellists and break out session leads:

Plenary sessions

Aneta Tyszkiewicz (European Federation Pharmaceutical Industry Associations)
Lada Leyens (F. Hoffmann-La Roche)
Dimitrios Athanasiou (Eurordis)
Greet Musch (Federal Agency for Medicines and Health Products - AFMPS; Clinical Trial Coordination Group chair)
Quentin Le Masne (Merck)
Monique Al (CCMO, Netherlands)
Thorsten Vetter (European Medicines Agency)
Jonas Santiago (Food and Drug Administration - FDA)
Franck Devaux (Hôpital Universitaire Des Enfants Reine Fabiola - HUDERF, Ethic Committee - Belgium)
Solange Corriol-Rohou (AstraZeneca, IMI MOBILISE-D) (co-lead)
Scottie Kern (Critical Path Institute)
Laurent Servais (Oxford University)
Kate Lyden (Vivosense)
Jacoline Bouvy (NICE)
Gözde Susuzlu (European Patient Forum)
Silvia Garcia (European Federation Pharmaceutical Industry Associations)
Anja Schiel (Norwegian Medicines Agency, European Medicines Agency)
Johanna van der Bom (Leiden University Medical Centre - Ethic Committee)
Kyriacos Hatzaras (European Commission)

BOS 1

Ramona L. Walls (Critical Path Institute)
Jonathan Chainey (Genentech / Roche)
Peter Van Reusel (CDISC)
Zahra Karimaddini (F. Hoffmann La Roche)
Bert Hartog (Janssen Pharmaceuticals)
Shaksi Sardar (Critical Path Institute)
Elnaz Atabakhsh (Critical Path Institute)

BOS 2
David Nobbs (F. Hoffmann La Roche)
Walter Maetzler (University of Kiel – IMI IDEA-FAST)
Rinol Alaj (Regeneron)
Jesper Kjaer (Danish Medicines Agency – DkMA)
Florian Lipsmeier (F. Hoffmann La Roche)
Kirsten Taylor (F. Hoffmann La Roche)
Stefan Avey (Janssen Pharmaceuticals)

BOS 3
Mireille Muller (Novartis)
Francois Houyez (Eurordis)
Trishna Bharadia (Independent Patient Advocate)
Britt Dhaenens (Erasmus MC)
Maria Teresa Ferretti (Women's Brain Project)
Chris Roberts (Alzheimer Europe)
Jayne Goodrick (Alzheimer Europe)
Richelle Flanagan (My moves matter)

BOS 4
Christine Mayer-Nicolai (Merck)
Frederik Grell Norgaard (Danish Medicines Agency – DkMA)
Wolfgang Lauer (BfArM)
Michelle Tarver (Food and Drug Administration – FDA)
Salvador Figueroa (F. Hoffmann-La Roche)
Lesley Maloney (F. Hoffmann-La Roche)

BOS 5
Kai Langel (Janssen Pharmaceuticals)
Thorsten Vetter (European Medicines Agency)
Alison Bond (Amgen)
Cathelijne de Gram (Janssen Pharmaceuticals)
Paul Strijbos (F. Hoffmann La Roche)
Damien Eggenspieler (Sysnav)
Wim Dartee (Novartis)
Gul Erdemli (Novartis)
Jacoline Bouvy (NICE)
Lada Leyens (F. Hoffmann-La Roche)

BOS 6
Solange Corriol-Rohou (AstraZeneca, IMI MOBILISE-D)
Marco Viceconti (University of Bologna, IMI Mobilise-D)
Jesper Kjaer (Danish Medicines Agency – DkMA)
Anja Schiel (Norwegian Medicines Agency, European Medicines Agency)
Lindsay Kehoe (Duke University - Clinical Trials Transformation Initiative - CTTi)
David Nobbs (F. Hoffmann-La Roche)

BOS 7
Antonio del Santo (F. Hoffmann-La Roche)
Phil Tregunno (MHRA)
Marten Wendt (Swedish MPA)