Digital technologies:

Enabling evidence generation in clinical development for regulatory and reimbursement decisions – how are the regulatory and HTA landscapes adapting?

24-25th June 2021

Workshop Report

CIRS Centre for Innovation in Regulatory Science

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Section 1: Executive Summary

Background to the workshop

Digitisation and digital health technologies are transforming clinical development; companies, regulators and Health Technology Assessment (HTA) agencies are looking to derive actionable insights from the data being generated. This is providing potential opportunities across medicines research and development, review, reimbursement and in the post-approval space. Digital technologies can facilitate a better understanding of both the safety and effectiveness of medicines by generating insights on patient behaviours and care outcomes, either as part of clinical development process or in real-life settings. In the development space, they have enabled innovative trial designs to be considered through the utilisation of apps, wearables and digital biomarkers.

These digital opportunities have been accelerated by the ongoing pandemic, underpinning not only the conduct of clinical development but also data generation. Digital health technologies have changed how companies, regulators, HTAs and patients monitor, manage, predict and make decisions about healthcare.

Regulators and HTA agencies are actively evaluating how to both foster and adapt to ensure a suitable environment for digital innovation. Prior to the pandemic, this can be seen through legislation such as the 21st Century Cures Act in the US, along with regulatory agencies exploring how digital health technologies can enable integrating the “patient voice” or patient centricity into their decision making. Indeed, both US Food and Drug Administration (FDA) and European Medicines Agency (EMA), as well as some mid-sized regulatory agencies, are establishing frameworks to enable the use of digital technology by evolving their medical devices guidelines to encompass digital health software. Within HTA agencies, the National Institute of Health and Care Excellence (NICE) for example have developed an evidence standard framework for digital health technologies.

The question is how is the clinical landscape evolving with respect to digitalisation and digital health technologies post-pandemic? Indeed, at a CIRS workshop in December 2020 there was agreement that for the following areas, the use of digital technologies accelerated during the pandemic needs to be retained:

- Enablers of virtual or decentralised clinical trials and associated tools, including electronic Patient Reported Outcomes, telehealth, apps and site monitoring
- Use of apps (especially for the collection of safety data), digital tools, wearables, devices with digital software for pre/post-authorisation utilisation
- Common digital infrastructure and platforms for collaboration and work-sharing during the review, including cloud submissions.

The key challenge for digital technologies being used in clinical development is how to ensure they can provide regulatory and HTA grade outcomes that can be validated vs current clinical endpoints, as well as how software and its continuous evolution should be regulated. Indeed, what was identified at the CIRS 2020 workshop as regulatory challenges included inconsistency in digital practices; qualification, guidance, and expertise to accommodate rate of change to technological innovation; issues with data validity/integrity and security; and the ability of trial sites and investigators to utilise digital tools.

As regulatory and HTA agencies adapt to the use of digital technology in clinical development, how aligned are their requirements across jurisdictions and what are the opportunities for both stakeholders post-pandemic to ensure the power of digital technology can meet its potential in the development, review

and reimbursement space. The aim of this workshop is to provide a platform to discuss the utilisation of digital technologies for evidence generation in the clinical development space for regulatory and HTA decision making.

Workshop objectives

- Discuss how agencies and companies are currently developing the role of digital technology for evidence generation in clinical development for regulatory and HTA decision making.
- Identify the opportunities and how to reduce potential barriers going forward for evidence generated by digital technologies for use in the review and reimbursement of medicines.
- Recommend areas of work/research that could facilitate alignment across jurisdictions to ensure digital technologies maximise their potential within a fit-for-purpose regulatory and HTA environment.

Venue

This workshop was held virtually over two days; 24-25th June 2021.

Workshop Programme

Affiliations are stated as they were at the time of the meeting (24-25th June 2021).

Session 1: Digital technology: its use in the development, review and reimbursement decisions for new medicines – where are we?	
CIRS welcome and introduction	**Dr Neil McAuslane,** *Director, CIRS*
Session Chair introduction	**Prof Hans-Georg Eichler,** *Department of Clinical Pharmacology, Medical University of Vienna, Austria*
"Digital technology" in clinical development - what role is it playing in evidence generation for the review and reimbursement of new medicines? Where are we on the journey?	
Regulator perspective	**Dr Leonard Sacks,** *Associate Director for Clinical Methodology, Office of Medical Policy, FDA, USA*
HTA perspective	**Dr Sean Tunis,** *Past President, HTA international (HTAi)*
Company perspective	**Dr Patrick Brady,** *Vice President, Regulatory Affairs, Head Regulatory Policy & Intelligence, Bayer, Germany*
Regulation of software as a medical device from a global standpoint	**Adj Prof John Skerritt,** *Deputy Secretary for Health, Products Regulation, Department of Health, Australia*
Utilisation of big data as a platform for transforming real-world evidence (RWE) as part of a lifecycle approach to support regulatory and reimbursement decision making	**Jesper Kjaer,** *Head, Data Analytics Centre, Danish Medicines Agency (DKMA) and Co-Chair of Big Data Steering Group, Heads of Medicines Agencies (HMA)*
Session 2: Technology enabled clinical development to provide evidence to support regulatory and HTA/payer decisions	
Session Chair introduction	**Dr Claus Bolte,** *Head of Sector Marketing Authorisation, Swissmedic*
Clinical development case studies - how are digital technologies or tools being used today as part of evidence generation for regulatory and/or HTA decision making?	
Use of digital technology in registry-based randomised controlled clinical trials (R-RCT)	**Dr Jingyu (Julia) Luan,** *Regulatory Affairs Director, AstraZeneca, USA*
Development of patient-relevant novel endpoints	**Thibaud Guymard,** *Senior Director, Global Digital Innovation Officer for Biogen Healthcare Solutions, Biogen, France*
How mobile digital health technology tools are modernising clinical endpoints	**Dr Christian Gossens,** *Global Area Head Digital Biomarkers, F.Hoffmann-La Roche Ltd, Switzerland*
Decentralised trials	**Lina Aljuburi,** *Head, Regulatory Science and Policy, North America, Sanofi, USA*

Session 3: Digital technology used in clinical development for agency decision making: how are the agencies adapting?	
Session Chair introduction	**Dr Thomas Lönngren,** *Independent Strategy Advisor, PharmaExec Consulting AB, Sweden*
Digital technologies and an HTA evidence standards framework - what needs to be considered?	**Mark Salmon,** *Programme Director – Information Resources, NICE, UK*
Global alignment or evidence standards frameworks for digital tools utilised in clinical development to generate evidence for regulatory decisions - would this be beneficial and what needs to be considered?	
Regulatory perspective	**Dr Florence Butlen-Ducuing,** *Topic Lead in Psychiatry and Mental Health, Office of Therapies for Neurological and Psychiatric disorders, EMA*
Company perspective	**David Isom,** *Director, Regulatory Policy, Global Regulatory Affairs, Pfizer, USA*
Digital Health regulation - the view from the Asia-Pacific	**Prof John Lim,** *Executive Director, Centre of Regulatory Excellence (CoRE), Singapore*
Session 4: Use of digital technologies – are these changing how stakeholders engage?	
CIRS welcome and introduction to Day 2	**Dr Neil McAuslane,** *Director, CIRS*
Session Chair introduction	**Dr Siu Ping Lam,** *Director of Licensing Division, Medicines and Healthcare products Regulatory Agency (MHRA), UK*
Digital engagement of patients: how has its utilisation evolved to improve decision making and if so in what way?	
Patient perspective	**Valentina Strammiello,** *Head of Programmes, European Patients Forum*
Regulatory perspective	**Dr Andrew Potter,** *Mathematical Statistician, Food and Drug Administration, USA*
HTA perspective	**Lindsay Lockhart,** *Public Involvement Adviser, Scottish Medicines Consortium*
Company perspective	**Robyn Carson,** *Vice President, Patient-Centered Outcomes, AbbVie, USA*
Separate, aligned, converged, harmonised, collaborative, reliant – what is the stakeholder's expectation of the development and access landscape of the future for company, regulator, HTA and payer interactions?	
"Dynamic dossier" cloud based approach for submission of data to regulator and HTA agencies - what is the ROI for companies and agencies?	**David Dorsey,** *Director, Global Regulatory Policy and Intelligence, Janssen, USA*
Enabling the digital ecosystem to transform quality data and clinical insights into evidence for improved patient outcomes – what needs to be considered?	**Dr Virginia Acha,** *Global Lead, Global Regulatory Policy, MSD, UK*

Session 5: Breakout Discussions	
Introduction to breakout discussions	**Prof Stuart Walker,** *Founder, CIRS*
Breakout A: Utilisation of digital tools for evidence generation in clinical development to improve regulatory/HTA decision making – What is needed to ensure they are regulatory/HTA grade?	**Chair: Prof Hans-Georg Eichler,** *Department of Clinical Pharmacology, Medical University of Vienna, Austria* **Rapporteur: Megan Doyle,** *Policy Director, Global Regulatory & R&D Policy, Amgen, USA*
Breakout B: The development of a globally aligned digital practice framework for utilisation of digital tools in clinical development – what value would it seek to provide?	**Chair: Dr Nick Crabb,** *Programme Director, Scientific Affairs, NICE, UK* **Rapporteur: Lesley Maloney,** *Product Development, International Regulatory Policy - Digital Health, Genentech/Roche, USA*
Breakout C: How can common digital infrastructure and platforms for collaboration and work-sharing during review/reimbursement and post-approval be facilitated – What is needed within the digital ecosystem?	**Chair: Fabio Bisordi,** Global Head International Regulatory Policy, F. Hoffmann-La Roche Ltd, Switzerland **Rapporteur: Dr Ryan Hoshi,** *Director, Regulatory Policy and Intelligence, AbbVie, USA*
Breakout D: How are digital technologies being used to facilitate patient engagement strategies and the collection of patient-reported data – Do new strategies need to be considered, particularly during accelerated development and review?	**Chair: Dimitrios Athanasiou,** *Member of EMA Paediatric Committee and Eurordis; Board Member of World Duchenne Organization, European Patient Forum and Greek Patients Association* **Rapporteur: Saiza Elayda,** *Associate Director, Global Regulatory Policy, Merck & Co, USA*

Key points from presentations

Please note, affiliations are stated as they were at the time of the meeting (24-25th June 2021).

Session 1: Digital technology – its use in development, review and reimbursement decisions for new medicines – where are we?

Dr Leonard Sacks, *Associate Director for Clinical Methodology, Office of Medical Policy, FDA, USA*, gave a regulatory perspective on the role digital technology is playing in clinical development. Technology should not necessarily change *what* clinical feature is measured but it may change *how* it is measured. Technology enables several opportunities for evidence generation, such as making trials more convenient for patients but also comes with several challenges. Regulatory experience with digital technology to date has mostly been related to decentralised clinical trials and current regulations do not address technologies used to assess medical products. Going forward, it will be important for regulators to share experiences and implement agile procedures to adapt to more sophisticated technologies and to identify problems early and efficiently.

Dr Sean Tunis, *Past President, HTA international (HTAi),* gave a HTA perspective on the role digital technology is playing in clinical development. Results from an informal survey showed that the HTA community has limited familiarity with digital technologies used in clinical development and that clarifying terminology and concepts would be helpful. Digital technology can provide the types of outcomes information that HTA agencies and payers are looking for, however, harmonisation of measures and core outcome sets are important given the proliferation of digital measures.

Dr Patrick Brady, *Vice President, Regulatory Affairs, Head Regulatory Policy & Intelligence, Bayer, Germany,* gave an industry perspective on the role digital technology is playing in clinical development. Devices in clinical development can be categorised according to whether they are part of a commercial product, such as a standalone medical device or a medical device that is part of a combination product, or a non-commercial product, such as a device for drug application or a digital drug development tool (dDDT) used to evaluate a drug. Regulatory considerations for dDDTs include tool accuracy, reliability, context of use for the clinical outcome assessment, usability of the tool by the intent-to-treat population and the 'meaningfulness' of the measure identified or predicted. The use of a dDDT should be discussed as early as possible within a clinical programme, ideally before protocol design and taking into account patients' preferences.

Adjunct Prof John Skerritt, *Deputy Secretary for Health Products Regulation, Department of Health, Australia* gave an overview of the regulation of medical device software, which varies around the world, though the International Medical Device Regulators Forum (IMDRF) is working towards greater alignment in this area. Many software products being used in medicines development, clinical trials, real-world evidence and pharmacovigilance are classed as medical devices. However, software developer partners may be unaware of this, and drug developers are often less familiar with medical device regulation than medicines regulation. Developers and clinical triallists using commercial software products should familiarise themselves with regulatory requirements and ensure that these products have appropriate approval.

Jesper Kjaer, *Head, Data Analytics Centre, Danish Medicines Agency (DKMA) and Co-Chair of Big Data Steering Group, Heads of Medicines Agencies (HMA),* described how the EMA and HMA are working to leverage data as evidence for better regulatory decision making through pilot studies and the Data Analysis Real World Interrogation Network (DARWIN EU). The approach is to network and partner to deliver new medicines for patients with unmet needs and to optimise the safe and effective use of medicines on the market.

Session 2: Technology-enabled clinical development to provide evidence to support regulatory and HTA/payer decisions?

Dr Jingyu (Julia) Luan, *Regulatory Affairs Director, AstraZeneca, USA*, gave an overview of registry-based randomised controlled trials (R-RCT), which are growing in interest as reliance on real-world data increases. R-RCTs are prospective randomised trials that use a clinical registry for one or several major functions for trial conduct and outcomes reporting. The world's first indication-seeking R-RCT called 'Dapagliflozin Effects on Cardiovascular Events in Patients With an Acute Heart Attack' (DAPA-MI) is using two national cardiovascular disease registries to prospectively collect data on the effects of dapagliflozin on cardiovascular events in patients with an acute heart attack without known diabetes. The trial is also using innovative digital technologies, including SmartCap adherence monitoring, to enhance patient experience and reduce costs. Regulatory agencies around the world have been interested in and supportive of the innovative design of DAPA-MI.

Thibaud Guymard, *Senior Director, Global Digital Innovation Officer for Biogen Healthcare Solutions, Biogen, France*, described how the measurement of neurological diseases could be greatly improved with technologies such as apps, smartphones, and wearables. To evaluate meaningfulness of signals derived from digital sensors, a four-level framework may be useful that incorporates the meaningful aspect of health, concept of interest, outcome to be measured and endpoint. Knowledge sharing, collaboration and transparency are key to moving forward with digital measurements.

Dr Christian Gossens, *Global Head Digital Biomarkers, Roche, Switzerland*, described how mobile digital health technology tools, such as the Roche Parkinson's Disease app, are modernising clinical endpoints. The pharmaceutical industry is already leveraging digital technology for portfolio decision making, however, there are challenges for regulatory decision making and a lack of harmonisation on digital endpoints.

Lina AlJuburi, *Head, Regulatory Science and Policy, North America, Sanofi, USA,* explained that decentralised clinical trials do not necessarily mean that all trial-related procedures and data acquisition are taking place remotely; there can be a hybrid approach, which may be preferable as it facilitates options for different geographies, patients and trial sites. Patient centricity, confidence and engagement with regulators is key to success for decentralised trials. All stakeholders need to leverage the changing global environment going forward (pre-, during and post-pandemic).

Session 3: Digital technology used in clinical development for agency decision making: how are the agencies adapting?

Mark Salmon, *Programme Director – Information Resources, NICE, UK*, gave an overview of the NICE evidence standards framework for digital health technologies, which provides a common set of principles and gives a benchmark for evidence requirements for HTA and other domains such as interoperability and regulation. Considerations for an HTA evidence standards framework for digital health technologies include a system wide multi-agency approach, industry and other healthcare system partner engagement, being responsive to change, alignment/conformity with international standards and support for adoption for clinicians and patients.

Dr Florence Butlen-Ducuing, *Topic Lead in Psychiatry and Mental Health, Office of Therapies for Neurological and Psychiatric disorders, EMA,* gave an overview of EU regulatory frameworks relevant to digital health technologies including the Medical Devices Regulation and General Data Protection Regulation. To move forward with regulatory frameworks for digital heath technologies, it is important to have clear scope and definitions, a multidisciplinary approach, multi-stakeholder collaboration, a patient

centred approach that facilitates trust, regulatory science to inform about applications in medicines development and evaluation and a flexible/dynamic approach.

David Isom, *Director, Regulatory Policy, Global Regulatory Affairs, Pfizer, USA,* spoke about how many forums globally are working to advance acceptance of digital health technologies and methods to assure validity of digital endpoints. Regulatory frameworks that promote global alignment of evidence standards will facilitate the use of digital technologies for evidence generation in clinical development. It will be essential to take forward learnings from the COVID-19 pandemic, where regulatory flexibility helped to accelerate use of digital health technologies and companies shared non-competitive insights with each other as well as with regulators. In addition, opportunities to promote global harmonisation through the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) should be optimised.

Prof John Lim, *Executive Director, Centre of Regulatory Excellence (CoRE), Singapore,* presented the outcomes of a two-day virtual roundtable led by CoRE to discuss evolving issues in digital health regulation in the Asia-Pacific. The discussions highlighted the importance of patient engagement, regulatory convergence, reliance pathways, innovative risk-based frameworks and advancing digital trials and digital transformation in regulation. To advance digital health regulation in the Asia Pacific, it was recommended to promote regulatory cooperation, recognition and reliance; employ neutral multistakeholder platforms; increase capacity building and training; and promote public-private collaborations.

Session 4: Use of digital technologies – are these changing how stakeholders engage?

Valentina Strammiello, *Head of Programmes, European Patients Forum,* gave a patient group perspective on how digital engagement of patients has evolved to improve decision making. Patients' uptake of digital solutions relies on empowerment, health literacy and transparency and trust of health data governance. While there are challenges in the digital health space, such as late or no patient involvement, evidence-based decision making is growing and there are opportunities for change in the 'post-COVID world' and with the enforced application of EU Medical Devices Regulation.

Dr Andrew Potter, *Mathematical Statistician, Office of Biostatistics, Division of Biometrics, US FDA Center for Drug Evaluation and Research,* gave a regulatory perspective on how digital engagement of patients and patient-focused drug development (PFDD) has evolved. The FDA is building on the experience of its PFDD meetings to develop a series of methodological guidance to enable stakeholders to go beyond powerful patient narratives and collect data that can serve as study endpoints and be used as evidence for regulatory decision making. Available resources and recommendations should be leveraged to determine the appropriateness of digital health technologies in clinical development, and this should be discussed early and frequently with regulators.

Lindsay Lockhart, *Public Involvement Advisor, Scottish Medicines Consortium (SMC),* gave an HTA perspective on engaging patients with digital technology. The SMC has continued to involve patient group representatives in its processes during the COVID-19 pandemic by using a new virtual meetings environment, which has advantages, such as improved inclusivity, as well as disadvantages, such as difficulties 'reading the room'. Communication, collaboration and consultation with patient groups and committee members have been key to adapting to virtual meetings. Continuous evaluation and improvement will be important to ensure these stakeholders are supported to make informed decisions.

Robyn Carson, *Vice President, Patient-Centered Outcomes Research, AbbVie, USA,* gave a company perspective on engaging patients with digital technology. Digital health technologies can help to improve understanding of the patient experience and efficiently operationalise public health programmes. For

example, mobile apps for COVID-19 vaccination programmes have been developed that allow users to register and check in for their vaccination, access their vaccination record and share their experience on social media. The pharmaceutical industry plays an important role in turning data into something meaningful for decision making and must partner with other stakeholders to unlock the full potential of digital health technologies.

David Dorsey, *Director, Global Regulatory Policy and Intelligence, Janssen, USA,* gave an overview of Accumulus Synergy and its return on investment (ROI) for companies and regulators. Accumulus Synergy is a non-profit company working to transform the regulatory submission process by creating the first-ever global dynamic data exchange platform. For companies, the ROI of the Accumulus platform will be improved productivity and efficiency, while for regulators the ROI lies in the creation of new opportunities for more efficient engagement with fellow regulators, companies and others. The overarching ROI of Accumulus will be in value to patients, as improved speed-to-market will allow patients around the world to receive critical medicines and improved use of data will provide for enriched and more real-time regulatory decisions.

Dr Virginia Acha, *Global Lead, Global Regulatory Policy, MSD,* explained what needs to be considered to transform quality data and clinical insights into evidence for improved patient outcomes. There are challenges to transform data to evidence relating to research design and fit-for-purpose data, data quality and standards and interoperability. To overcome these challenges, there must be coordination and alignment internationally and across stakeholders, confidence-building measures and a learning focus where positive and negative experiences are shared. The regulatory discipline must have willingness, organisational capabilities and common standards and platforms to adapt to digitally sourced and transformed data.

Session 5: Breakout discussions

A) Utilisation of digital tools for evidence generation in clinical development to improve regulatory/HTA decision making – what is needed to ensure they are regulatory/HTA grade?

This breakout group identified opportunities for digital tools in clinical trial logistics, endpoints, regulatory/HTA coordination, prioritisation of stakeholder preferences, patient engagement and patient data. Key challenges were thought to be conservatism/scepticism towards digital tools and lack of regulatory/HTA standards. Suggested solutions for these challenges included publishing case studies and developing guidance for digitally derived endpoints that fall outside of existing biomarker and Clinical Outcome Assessment guidance.

Recommendations for CIRS and/or other groups:

1. Engage with stakeholders to coordinate a way forward, building on discussions from this workshop:
    - Surveys of companies for case studies
    - Surveys of what digital tools have already been successfully used in the past 3-4 years
    - Identify via research/publications what validated endpoints for digital technologies exist.
2. Coordinate interactions on the development of standards across HTA bodies and regulators.
3. Engage patient groups to see what is relevant to them in various therapeutic areas.

B) Development of a globally aligned digital practice framework for utilisation of digital tools in clinical development – what value would it seek to provide?

This breakout group concluded that the value for such a framework would lie in reducing inefficiencies and supporting efforts to engage a greater variety of patients in drug development efforts, which supports the end goal of delivering personalised healthcare and improved patient outcomes at a reduced cost to society. Domains that would need to be considered in the framework would be clarity of evidence required for validation of digital health technologies and endpoints; ability to measure what is meaningful to patients; new ways for regulators to engage across jurisdictions and across regions; and global harmonisation of standards and pathways for acceptance of digitally derived endpoints.

Recommendations for CIRS and/or other groups:

1. Conduct a landscape analysis/maturity model assessment for digital health, with specific emphasis on use of digital health technologies to develop endpoints for use in drug development and in regulatory decision making.

2. Encourage development of global workstreams on digital practice frameworks, whether through ICH or other means, to align terminology, validation requirements and globally harmonised pathways and approaches.

C) How can common digital infrastructure and platforms for collaboration and work sharing during review/reimbursement and post-approval be facilitated – what is needed within the digital ecosystem?

The breakout group agreed that a common digital infrastructure would be helpful for promoting regulatory reliance, improving data accessibility, enabling collaboration, increasing harmonisation and accelerating patient access. Challenges that were identified included trust, interoperability, data governance, global harmonisation, resources and training.

Recommendations for CIRS and/or other groups:

1. Benchmarking or landscaping analysis of current policies and regulations regarding the use of digital infrastructure e.g. use of digital health technology, data policy, data security, data privacy. Existing benchmarking studies and learnings from other fields/industries should be leveraged to develop best practices.
2. Additional workshops on related or more specific/granular topics on the use of digital infrastructure.
3. What are the minimum resources, tools and best practices that emerging regulators would need in order to leverage common digital infrastructure technologies?

D) How are digital technologies being used to facilitate patient engagement strategies and the collection of patient-reported data – do new strategies need to be considered, particularly during accelerated development and review?

This breakout group agreed that social media, mobile applications and wearables were impactful tools that should be prioritised under accelerated development and review timelines. Identified challenges to using digital technologies for patient engagement included accessibility, transparency, trust and following up with patients on how their data/input was used to inform decision making or direct research.

Recommendations for CIRS and/or other groups:

1. Further discussion on policy and regulatory framework development
2. How to tie measurements by regulators or industry to what matters to patients
3. Development of new methodologies for validation of Patient Reported Outcomes (PROs)
    a. PRO science – creating benchmarks for day-to-day use by clinicians
4. How to account for disparities among cultures and different socioeconomic populations

Section 2: Presentations

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Technology-enabled clinical trials

"Digital technology" in clinical development - what role is it playing in evidence generation for the review and reimbursement of new medicines? Where are we on the journey?

Regulator perspective

Dr Leonard Sacks, *Associate Director for Clinical Methodology, Office of Medical Policy, Center for Drug Evaluation and Research (CDER), FDA, USA*

While electronic technologies have been used for many years to make measurements that support the approval of drugs, there is currently a revolution in miniaturised digital technologies that allow acquisition of data from patients remotely. These technologies include wearable sensors, environmental sensors, smartwatches, tablets and mobile phones with supporting applications. These are increasingly being used in clinical practice and as 'wellness' products to promote activity and wellbeing. In addition, they have a wide range of roles in evidence generation, for example by facilitating patient identification and selection, enrichment of populations, subgroup analysis, measuring drug efficacy and/or safety, dose ranging studies, and natural history studies.

Technology is only a tool to measure clinical features; technology should not necessarily change *what* is measured but it may change *how* it is measured. For this reason, the terms 'digital endpoints' and 'digital biomarkers' can be misleading, as they are digital measurements of clinical endpoints. It is important that clinical features remain clinically meaningful, and that technology is verified and validated to ensure accuracy and reliability, particularly if not supervised by study personnel.

Opportunities and challenges for evidence generation

Technology enables several opportunities for evidence generation, such as making trials more convenient for patients, particularly those with rare diseases, mobility challenges, cognitive challenges or domestic challenges; continuous or frequent data collection; capturing rare events; capturing functionality in the real-world environment; and collecting pharmacodynamic data during the dosing cycle. In addition, there are opportunities in the use of interactive apps that have been developed to challenge patient performance, for example, an app has recently been developed with audio, visual and coordination tests for Parkinson's disease. The challenges of using digital technology for evidence generation relate to reliability, sensitivity, specificity, missing data, clinical meaning (new endpoint vs existing endpoint), patient safety, patient retention, privacy and security, and data provenance and custody.

Regulatory considerations

Current regulations in the US do not address technologies used to assess medical products. Regulations require data "from which experts can reasonably conclude that a drug has its intended effects", so data reliability is central when it comes to digital health technologies (DHT). Suitability for a clinical trial must be determined independent of whether the DHT was cleared by the FDA Center for Devices and Radiological Health (CDRH). Informed consent must describe expectations of privacy, any physical risks and address expectations of real-time safety monitoring. Requirements for the FDA Code of Federal

Regulations Title 21 Part 11 refer mainly to custody of data, access controls, audit trails and the preservation of source information.

Where are we now?

Regulatory experience with digital technology to date has mostly been related to decentralised clinical trials, which have become increasingly important due to the ongoing COVID-19 pandemic. The FDA guidance "Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency" permits remote patient visits using video or audio technology and electronic informed consent using electronic web-based or mobile phone-based platforms.

DHTs have not yet been used in primary assessments of outcome, though there is a lot of development work ongoing. The FDA has some experience with digital patient-reported-outcomes using portable tablets and the 2017 approval of velbenazine, a drug for tardive dyskinesia, was partly supported by video recordings of patients' movements that were then blinded and analysed by experts.

The FDA has issued guidance on electronic source data, electronic informed consent, use of electronic records and electronic signatures. Guidance for decentralised trials and DHTs is currently being prepared.

Looking ahead

Going forward, it will be important to share experiences with DHTs among regulatory agencies throughout the world since so many trials are now international. Developing specifications for technologies may be important to ensure quality and reliability of data from DHTs used in different settings. Systems used for telemedicine activities are likely to become more sophisticated and hopefully more secure in future. Regulatory agencies will need agile procedures to adapt to better systems and technologies and to identify problems early and efficiently. It is likely that in 5-10 years, the time and cost of clinical trials will become more manageable as the power of technological tools is employed.

HTA and digital technology: beginning the journey

"Digital technology" in clinical development - what role is it playing in evidence generation for the review and reimbursement of new medicines? Where are we on the journey?

HTA perspective

Sean Tunis, *Past President, HTA international (HTAi) and Principal, Rubix Health*

An informal survey of HTA experts revealed that there is confusion amongst the HTA community about terminology used in the digital space; many respondents assumed that 'digital technology' referred to digital therapeutics or software-enhanced diagnostics. While the HTA community is familiar with digital therapeutics and diagnostics, many have not given much thought to digital technology for clinical development.

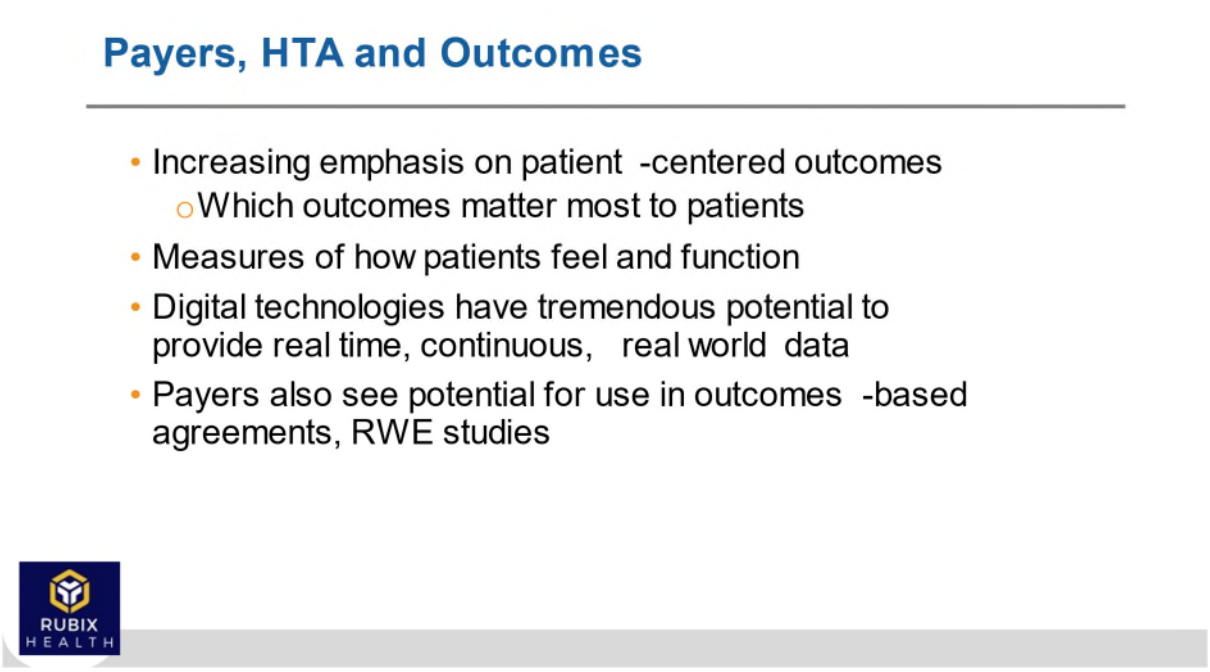
Clarifying terminology and concepts is therefore important when discussing digital technologies with different stakeholders. The Digital Therapeutics Alliance has established three categories of digital technologies [1], including useful definitions that could be more widely adopted:

- digital health - covering data and information capture, storage, transmission, and display products e.g. telehealth, lifestyle apps, fitness trackers.
- digital medicine – measurement and intervention products e.g. digital diagnostics, digital biomarkers, remote patient monitoring.
- digital therapeutics – therapeutic intervention products that may treat/manage/prevent disease or improve a health function.

Digital technologies have tremendous potential to provide real time, continuous data about how patients feel and function in the real world. This could be very valuable for HTA agencies and payers, who are placing increasing emphasis on patient-centered outcomes in their assessments. In addition, digital technology has great potential for use in outcomes-based agreements and Real-World Evidence (RWE) studies.

HTA agencies and payers always compare products with alternatives, which is much easier when the same outcomes are measured with the same instrument and at the same time points. Digital technology has great potential to help with this through the use of digital biomarkers in core outcomes sets, which are defined as an "agreed standardised set of outcomes that should be measured and reported, as a minimum, in all clinical research in specific areas of health or health care" [2]. However, there is a need for harmonisation to ensure that the digital biomarkers HTA are being presented with are the most patient centric.

In summary, the HTA community has limited familiarity with digital technologies, so clarifying terminology and concepts will be helpful. Digital technology can provide the types of outcomes information that HTA agencies and payers are looking for, however, harmonisation of measures and core outcome sets will be important given the proliferation of digital measures.



References:

[1] Digital Therapeutics Alliance. https://dtxalliance.org/

[2] Core Outcome Measures in Effectiveness Trials (COMET) initiative. https://www.comet-initiative.org/

Digital technology in clinical development

What role is it playing in evidence generation for the review and reimbursement of new medicines? Where are we on the journey?

Company perspective

Dr Patrick Brady, *Vice President of Global Regulatory Affairs and Head of Regulatory Policy and Intelligence, Bayer, Germany*

Digital technologies have changed the conduct of medicine and clinical trials, but without altering the primary purpose, for example, to communicate with patients or to measure a specific clinical function. The use of connected digital products in clinical research has grown dramatically over the last twenty years and continues to increase during the COVID-19 pandemic.

Even before the pandemic, there was a need for greater efficiency in clinical trials; 80% of clinical trials were delayed due to recruitment problems, dropout rates were around 30%, 85% of trials failed to retain a sufficient number of patients and 70% of potential participants live more than two hours away from their nearest study site [1]. At the start of the COVID-19 pandemic, up to 90% of clinical trials were delayed and regulators were open to ideas on how keep clinical research going [1]. With this came the opportunity to accelerate the use of decentralised clinical trials, which address trial inefficiency in patient-centric ways.

What are digital tools?

Devices in clinical development can be categorised according to whether they are part of a commercial product, such as a standalone medical device or a medical device that is part of a combination product, or a non-commercial product, such as a device for drug application or a digital drug development tool (dDDT) used to evaluate a drug. The FDA defines dDDTs as “methods, materials, or measures that can aid drug development and regulatory review”. dDDTs are a key feature in many decentralised clinical trials and in most cases, they are wearable devices. In the US, the dDDT may be an approved/cleared medical device and in the EU, the dDDT must have a CE mark. In both regions, the dDDT must be qualified for its intended use in the clinical trial.

Bayer is working on the verification, analytical validation and clinical validation of different dDDTs in trials for heart failure (see below). Regulatory considerations for dDDTs include tool accuracy, reliability, context of use for the clinical outcome assessment, usability of the tool by the intent-to-treat population and the ‘meaningfulness’ of the measure identified or predicted.

What does the regulatory landscape look like?

Digital tools are regulated through:

- medical devices legislation, such as the EU Medical Device Regulation 2017/745 and the US Code of Federal Regulations Title 21;
- FDA 21st Century Cures Act, section 507 Federal Food, Drug, and Cosmetic Act (FD&C Act), which states that DDTs need to be "qualified" for application in clinical investigation;
- ICH guidance for good clinical practice E6 (R2), which defines requirements for computerised systems and tools for clinical trials;
- ethical aspects, such as ISO 14155 (Clinical investigation of medical devices for human subjects – Good Clinical Practice);
- data protection laws.

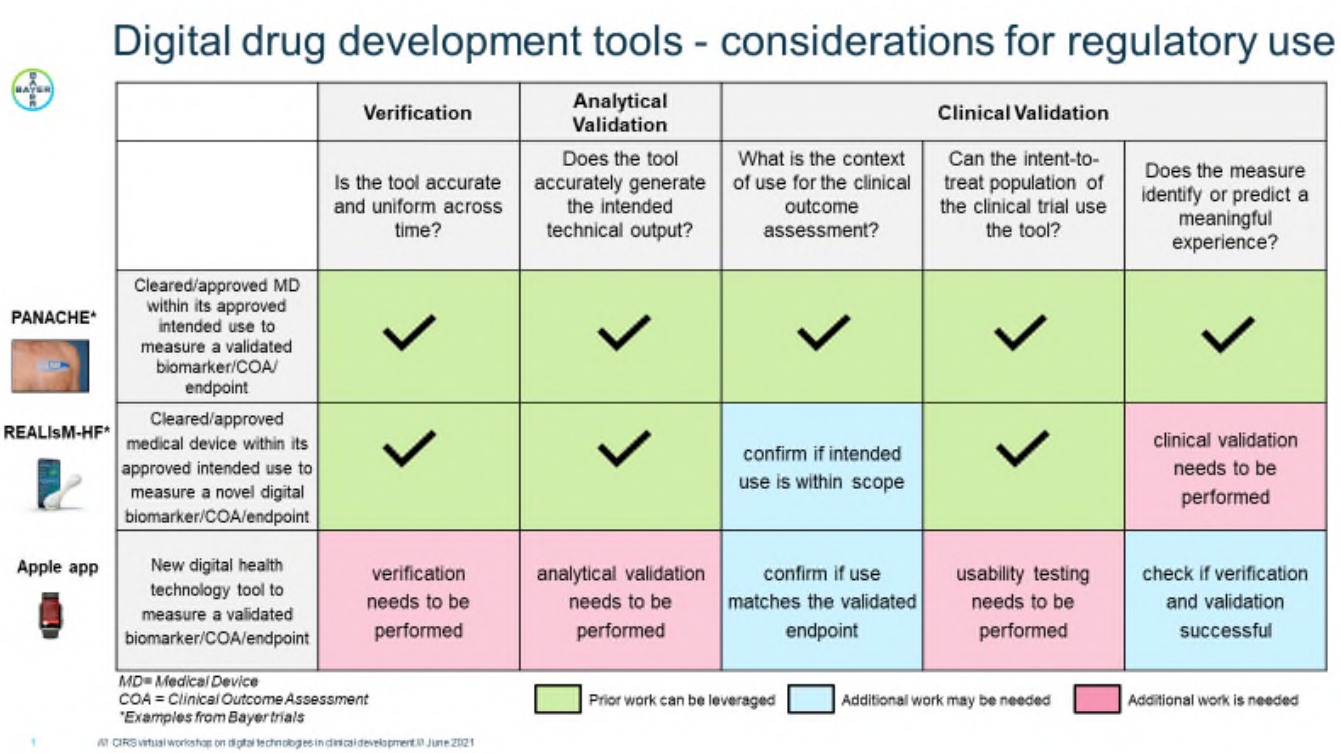
While data obtained by medical devices is protected by patient privacy laws, such as the Health Insurance Portability and Accountability Act (HIPAA) in the US, those same protections do not apply to consumer-grade wearable devices like fitness trackers. In the EU, the General Data Protection Regulation (GDPR) does not distinguish between device type and requires that all data generated by wearable devices or apps have clearly defined purposes for use and users.

Integrating the voice of patients

Industry must work in collaboration with patients and doctors to ensure that their perspectives, needs and abilities are considered when using digital tools in clinical development. This includes patients' preferences for personal interactions with healthcare professionals, clear information and connection with other patients who have participated in clinical trials. The diversity of patient populations should also be acknowledged; nearly 7% of Americans do not have internet access and this is linked to factors such as age, educational attainment, and household income [2]. It is important to recognise that some people are not comfortable with connected devices, some diseases require in-person visits, and some parameters cannot be measured remotely. Digital tools should be a facilitator, not a source of anxiety for patients.

Summary

Digital technologies present an opportunity for innovative thinking in clinical trials, though it is important that digitalisation does not lead to dehumanisation and that patients' preferences continue to be considered. The use of a DDT should be discussed as early as possible within a clinical programme, ideally before protocol design. The world is currently in a dynamic time where regulators are helping to enable new frameworks; this sense of urgency should be maintained beyond the COVID-19 pandemic.



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Regulation of medical device software

Adjunct Prof John Skerritt, *Deputy Secretary for Health Products Regulation, Department of Health, Australia*

Software products are increasingly used in medicines development, clinical trials, real-world evidence and pharmacovigilance. Many of these products are classed as medical devices, but software developer partners may be unaware of this, and drug developers are often less familiar with medical device regulation than medicines regulation. Software as a Medical Device (SaMD) is defined as any form of software that runs on a general-purpose platform e.g. on a laptop, tablet or mobile phone, on a server, web application or cloud platform. In Australia, software is defined a medical device when the manufacturer intends for its product to be used for diagnosis, prevention, monitoring, treatment, or alleviation of disease, injury or disability.

Why regulate software?

SaMD regulation assures that products work as intended and are clinically safe. Despite the risk of poor performance for software being just as great (or greater) than for physical devices, often developers have not done thorough clinical trials on software devices and apps versus other devices. There is also limited information in refereed literature on clinical or analytical validation for some SaMD, and while products are improving, there are several examples of products incorrectly diagnosing or monitoring serious conditions e.g. melanoma, arrhythmia or diabetes [1,2].

Global regulation of SaMD

Regulatory schemes for SaMD vary around the world, for example, the emphasis placed on quality management systems (QMS) differs between countries. However, the International Medical Device Regulators Forum (IMDRF) is leading greater alignment in the regulation of SaMD and clinical evaluation approaches for software are converging globally. Software risk classification is generally determined by the seriousness of the condition being diagnosed or managed and the significance of the information being provided for the healthcare decision.

Artificial Intelligence (AI) adds an additional challenge to SaMD regulation and is currently being discussed by IMDRF to develop aligned guidance. The EU has proposed an economy-wide approach to AI regulation and the US FDA is currently exploring draft guidance for AI-based software.

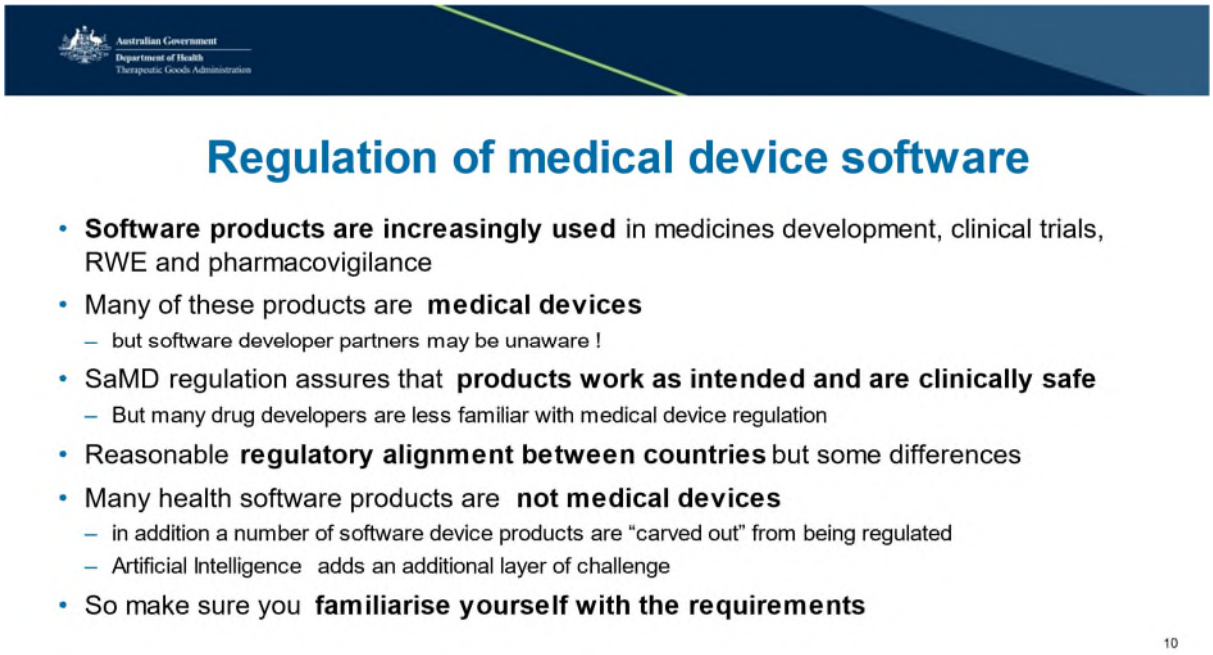
Software is regulated under general medical device schemes, but with some regulatory fine tuning. Additional requirements for regulatory submissions have been implemented for management of data and information, including cyber security; development, production, and maintenance; and the current version and build number for the software to be made identifiable to users. Classification rules may also be different for software intended for diagnosing and screening for a disease versus monitoring progression of the disease or specifying or recommending a treatment or providing therapy (via provision of information). Differences between the intended end users (consumers versus health professionals) also impact classification and therefore the level of regulatory oversight needed.

Many regulators ‘carve out’ particular software types from regulation as a device if the software product presents a very low risk to safety or if alternative oversight schemes are in place. The scope of ‘health software’ is broader than ‘medical device software’; most health software is not a medical device and is not regulated by most agencies. Examples of ‘carved-out’ software in some countries include consumer health products such as health preventative and management devices that do not provide specific treatment suggestions; enabling technology for telehealth, remote diagnosis, healthcare or dispensing; digitisation such as simple dose calculators and Electronic Patient Records; analytics, such as population

based analytics for assessing cohorts; Laboratory Information Management Systems; and Clinical Decision Support Software that is not intended to replace health professional judgement in making a diagnosis or treatment decision.

Advice for developers

Drug developers and clinical triallists using commercial software products should check that these products have appropriate regulatory approval. This will help to ensure that the developer's Good Clinical Practice status for the conduct of their clinical trials is not at risk. If an in-house or bespoke software product is being used, it is important to determine if the product is a medical device and its risk classification. The developer must also hold evidence of compliance with the essential principles for safety, quality, and performance; obtain third-party certification for assessment of technical files, inspection of QMS and the manufacturing site; apply for regulatory approval; and follow post-market requirements.



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Utilisation of 'big data' as a platform for transforming real-world evidence (RWE) as part of a lifecycle approach to support regulatory and reimbursement decision making

Jesper Kjaer, *Head, Data Analytics Centre, Danish Medicines Agency (DKMA) and Co-Chair of Big Data Steering Group, Heads of Medicines Agencies (HMA)*

EMA and HMA are working to leverage data as evidence for better regulatory decision making through pilot studies and the Data Analysis Real World Interrogation Network (DARWIN EU). The approach is to network and partner to deliver new medicines for patients with unmet needs and to optimise the safe and effective use of medicines on the market.

Pharmacovigilance Risk Assessment Committee (PRAC) pilot

The PRAC pilot aimed to test the feasibility and usefulness of a rapid data analysis process making use of Real-World Evidence (RWE). This process consisted of three stages: topic identification and feasibility, in which PRAC members could propose topics and provide input; data analysis, in which PRAC members could comment on the protocol and then analysis was carried out by EMA; and reporting, where PRAC members received the results and had an opportunity to assess them as external evidence.

12 requests for analyses were received through the PRAC pilot, 7 of which were agreed following proactive proposal from EMA on confirmed signals or referral, and 5 of which were received directly from PRAC members. Two thirds of the requests for analyses were considered useful for regulatory decision making and were finalised into a report for discussion by the PRAC. The process took a median of 88 days from request to final report, with a range from 26 to 138 days.

Big data work plan

The HMA-EMA Joint Big Data Taskforce developed ten priority recommendations, which are at various stages of implementation:

Recommendation	Progress
1. Deliver a **sustainable platform** to access and analyse healthcare data from across the EU (Data Analysis Real World Interrogation Network (DARWIN EU)).	Project funding strategy has been established and a 'call for tender' recently opened to select a service provider to establish the DARWIN EU Coordination Centre.
2. Establish an EU framework for **data quality** and representativeness.	Procurement launched for an academic consortium to deliver a data quality framework. Draft data quality framework should be available early 2022.
3. Enable **data discoverability**.	Workshop on RWE meta data held in April and on track to have agreed meta data by the end of the year. Will support future European inventory of real-world data (RWD).
4. Develop EU **Network skills** in Big Data.	Skills survey completed on RWE statistics and data science (800+ responses). Clear priorities identified for training.

Recommendations (continued)	Progress (continued)
5. Strengthen EU **Network processes** for Big Data submissions.	PRAC pilot of rapid analysis of RWD completed. Review of 2018/2019 marketing authorisations and RWE completed. Big data topics included in the 2021 work plans of the Committee for Medicinal Products for Human Use (CHMP), PRAC, Committee for Advanced Therapies (CAT), Committee for Orphan Medicinal Products (COMP) and Paediatric Committee (PDCO).
6. Build EU Network **capability to analyse** Big Data (technology / analytics).	Retrospective review of experience with raw data from clinical trials completed. Pre-pilot of raw data analysis at CHMP ongoing.
7. Modernise the delivery of **expert advice**.	Establishing a multidisciplinary 'methodologies' working group.
8. Ensure data are managed and analysed within a **secure and ethical governance** framework.	Recommendations on ethics advice (to leverage existing structures). Question and answer on data protection is in progress.
9. Engage with **international initiatives** on Big Data.	Data Standardisation Strategy for the Network is under development (workshop held in May 2021). Good progress is being made with the US FDA and Health Canada on developing a Real-World Evidence Collaboration Roadmap.
10. Establish an EU Big Data '**stakeholder implementation forum**'.	Following a successful stakeholder workshop in December 2020, three technical workshops have been held so far in 2021 and planning is ongoing for further technical workshops and a multi-stakeholder forum on Big Data later in 2021.

DARWIN EU network

The EU has a rich healthcare data environment but access to data is currently limited and analysis processes are slow and complex. DARWIN EU will help to address this issue by establishing and maintaining a secure EU data platform that supports better decision-making throughout the product lifecycle with reliable evidence for real-world healthcare. DARWIN EU is a Federated Network of Data Holders and expertise, exposing data using a common data model and working under a common governance, set of standards and service levels with regards to studies and analysis of data. A Coordination Centre acts as the entry point into this federated network and manages the network on behalf of EMA and the European Medicines Regulatory Network (EMRN), while EMA has strategic control and oversight of operations.

Principal benefits of DARWIN EU relate to the national and EU regulation of medicines. For example, there will be benefits in drug development (disease epidemiology, unmet need, historical controls, planning); authorisation (contribution to benefit-risk, controls, extrapolation to general and special populations); and on market (benefit risk monitoring, extension of indication). Additional benefits will come as EU partners participate and access the platform, including:

- the European Commission as it delivers on European Health Data Space;
- national governments to support health policy and delivery of healthcare systems;

- HTA bodies and payers to support better quality decisions on cost-effectiveness;
- EU health agencies, giving use cases specific for the European Food Safety Authority, European Center for Disease Prevention and Control, European Chemicals Agency and Joint Research Centre;
- EU patients who will benefit from faster access to innovative medicines and safe and effective use.

HMA

EUROPEAN MEDICINES AGENCY

What is DARWIN EU - a network not a database

- DARWIN EU is :
  - A **Federated Network of Data Holders and expertise**, exposing data using a common data model and working under a common governance, set of standards and service levels with regards to studies and analysis of data.
  - A **Coordination Centre** that acts as the entry point into this federated network and manages the network on behalf of EMA and the EMRN.
  - **EMA with strategic control and oversight of operations**, e.g. interface with EMA committees, EMA own analysis, driving standards, specifications, guidelines, management of the coordination centre.

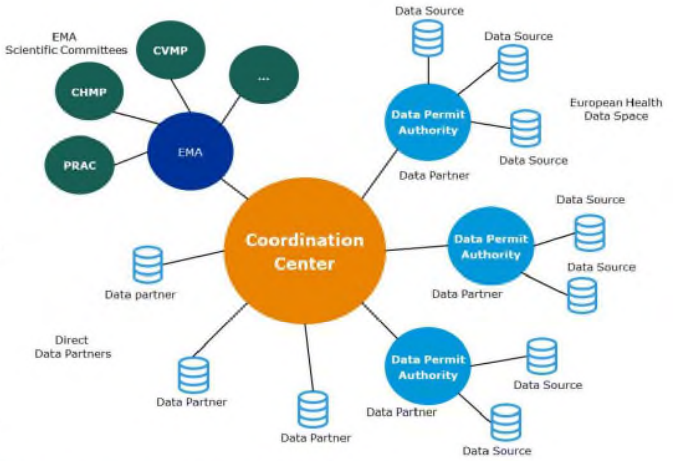

Figure 1 provides a high-level representation of the DARWIN EU® network.

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Classified as public by the European Medicines Agency

Use of digital technology in a registry-based randomised controlled trial (R-RCT)

Jingyu (Julia) Luan, *Global Regulatory Affairs Director, AstraZeneca, USA*

Reliance on real-world data (RWD) increases as trials move from traditional randomised controlled trial (RCT) designs towards more pragmatic studies. Although pragmatic studies alone are not enough for registration purposes, and are unlikely to be in the near future, there is growing interest in pragmatic trials, which are designed to evaluate the effectiveness of interventions in real-life routine practice settings.

What is an R-RCT?

A registry-based randomised controlled trial (R-RCT) is a prospective randomised trial that uses a clinical registry for one or several major functions for trial conduct and outcomes reporting. An R-RCT is a hybrid of an RCT and pragmatic clinical trial model and utilises the strengths of both models so that it is randomised, facilitates causal interference, measures efficacy, uses a broad population, has high external validity and is resource effective.

Key features of an R-RCT include study visits that align with clinical routine; data collection through a registry that is also used for the study; and study-specific data is collected via the registry interface. This has advantages such as fewer visits and no duplicate data collection; reduced patient and investigator burden; and more clinical trials at lower cost within a shorter time period.

Example of an R-RCT: DAPA-MI

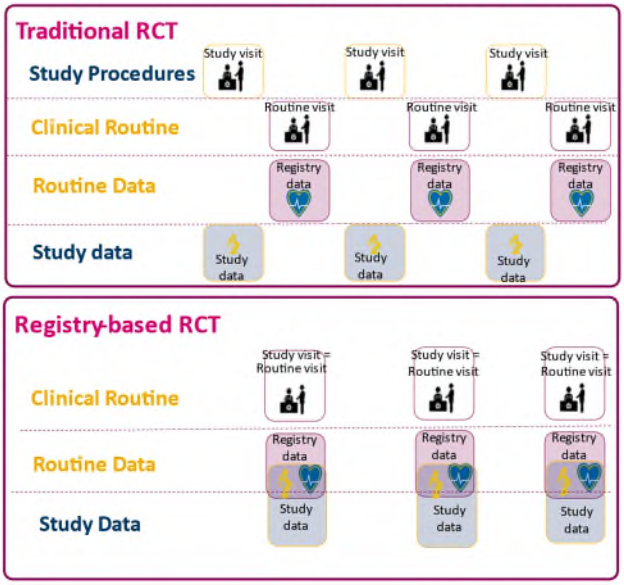
'Dapagliflozin Effects on Cardiovascular Events in Patients With an Acute Heart Attack' (DAPA-MI) is the world's first indication-seeking R-RCT, which will examine the effects of dapagliflozin on cardiovascular events in patients with an acute heart attack without known diabetes. It will recruit around 6400 patients from approximately 50 hospitals in Sweden and 50 hospitals in the UK. Prospective data collection will be conducted using two national cardiovascular disease quality registries, SWEDEHEART, hosted by Uppsala Clinical Research Center in Sweden, and MINAP, hosted by the National Institute for Cardiovascular Outcomes Research in the UK. It is hoped that for DAPA-MI, efficient data collection will lead to a lower per patient cost and higher recruitment speed.

Regulatory agencies around the world have been interested in and supportive of the innovative design of DAPA-MI. The trial has been discussed in formal scientific advice meetings with five agencies (UK, USA, Sweden, Germany and EU) as well as two workshops with agencies in Brazil and Japan. DAPA-MI has been granted FDA Fast Track Designation and Special Protocol Assessment Agreement, which confirms that it is adequately designed to address scientific and regulatory requirements for a registrational study.

Use of digital technologies

The DAPA-MI trial is using innovative digital technologies to enhance patient experience and reduce costs per patient without impacting timelines. The two population registries being used will not only help to accelerate patient recruitment but also reduce patient and investigator burden by facilitating automated data transfer from routine clinical appointments. In addition, DAPA-MI uses a patient app for remote patient monitoring and information sharing as well as SmartCap adherence monitoring technology. Whenever a SmartCap bottle is opened, a signal is sent to the database in real time; if the SmartCap remains unopened for some time, the patient's healthcare professional will be alerted so that they can follow up with the patient.

Key Features and Advantages of R-RCT



Key Features of R-RCT:

- Study visits align with clinical routine
- Data collected through registry also used for study
- Study specific data collected via registry interface

Key Advantages of R-RCT:

- Fewer visits and no duplicate data collection
- Reduce patient and investigator burden
- More clinical trials at lower cost within shorter time period
- For DAPA-MI, efficient data collection leads to a lower per patient cost and higher recruitment speed

Digital measurements to improve clinical development of medicines in neuroscience

Development of patient-relevant novel endpoints

Thibaud Guymard, *Senior Director, Global Digital Innovation Officer for Biogen Healthcare Solutions, Biogen, France*

Digital solutions could enable better measurement of meaningful aspects of health in the clinical development of medicines. They offer a **patient centric approach**, through clinical outcomes that are relevant to people living with the disease and measures that are performed in a daily living environment; **high-quality measures**, which may be more sensitive measures of disease activity compared to traditional scales, potentially enabling faster and more objective readouts in clinical trials; and **recognised endpoints**, which support company decision making on major research and development phases e.g. moving from phase I to phase II. However, a question remains over whether these endpoints are recognised in regulatory and reimbursement decisions.

Transforming neurological assessments

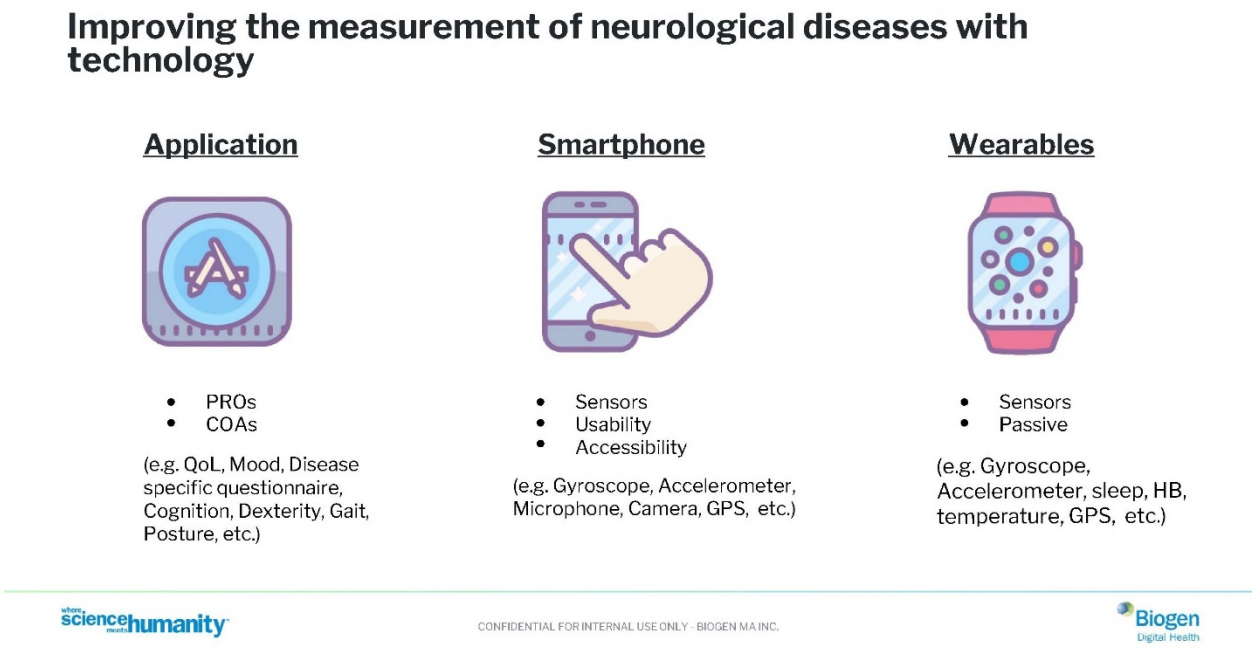
The measurement of neurological diseases could be greatly improved with technologies such as apps, smartphones, and wearables. For example, smartphones can have functions to assess gaze and facial expression using visible and infrared cameras; mobility can be assessed through inertial measurement units, such as an accelerometer; fine motor control measured using pressure and touch functions; and speech/voice assessed using the microphone. Apps often focus on the collection of patient-reported outcomes (PROs) and clinical outcome assessments (COAs), such as quality of life, mood, cognition, dexterity, gait, and posture. While both smartphones and wearables have sensors that allow passive or active monitoring, smartphones may be a more accessible and user-friendly option for most patients.

The six-minute walk test is a widely used aerobic assessment for neurological diseases, however, it does not consistently correlate with clinical endpoints such as mortality or disease progression and is not considered meaningful by patients. To evaluate meaningfulness of signals derived from digital sensors, the following four-level framework is useful [1]:

1. Meaningful aspect of health e.g. for someone living with multiple sclerosis, the ability to perform ambulatory activities
2. Concept of interest e.g. walking capacity
3. Outcome to be measured e.g. duration of walking bouts per day
4. Endpoint e.g. duration of walking bouts per day

Looking to the future

To move forward with digital measurements, learnings from the COVID-19 pandemic in relation to remote studies and real-world data should be shared and implemented. Transparency should be facilitated to avoid duplication and priority areas from regulators and HTA agencies should be shared to encourage broader collaboration. There must also be clarity on how sponsors pursue dialogue outside of formal regulatory qualification procedures in order to address complex issues associated with digital solutions.



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How mobile digital health technology tools are modernising clinical endpoints

Dr Christian Gossens, *Global Head Digital Biomarkers, Roche, Switzerland*

Most molecules fail to make it through development to launch, with 79% of clinical failures attributable to safety or efficacy [1]. Failures to prove efficacy could potentially be due to an inability to measure a meaningful treatment effect. Current clinical outcome assessments have challenges with **frequency**, for example, fluctuating symptoms may be mischaracterised by infrequent assessment at clinic visits; **precision**, as clinically meaningful differences may be masked by low resolution scales; **accuracy**, as subjective judgement of symptom severity may lead to inaccurate measurement and placebo effects; **reliability**, as patients/caregivers may have short recall periods meaning ratings are inconsistent over time; and **ecological validity**, as patients may present to the clinician or perform differently in the clinic compared to real life. Digital health technology tools can help to address these challenges.

Parkinson's mobile app

In 2014, Roche first started developing a mobile application to measure outcomes in Parkinson's disease (PD) objectively. Now in its third generation, the Roche PD app has active tests that measure a range of disease aspects such as cognition, speech, bradykinesia (slowness of movement), dexterity, tremor etc; surveys collecting patient-reported outcomes (PROs) and quality of life measures; passive monitoring of gait, mobility and sociability; and in-clinic tests that help to validate the unsupervised digital home testing.

Clinical studies using the Roche PD app have demonstrated that the mobile sensor measures correlate with clinical gold standard tests. Frequent sampling enabled measurements of rest tremor symptoms before/after sporadic clinic visits and the sensors were able to detect significant rest tremor in patients clinically scored as having no tremor [2]. This heightened sensitivity to motor symptoms will help to measure progression of PD, especially in patients with early symptoms.

A Study to Evaluate the Efficacy of Prasinezumab (RO7046015/PRX002) in Participants With Early Parkinson's Disease (PASADENA) was a randomised, double blind, placebo-controlled phase II trial that did not meet its primary endpoint. However, analysis of secondary and exploratory endpoints revealed that there was a reduced clinical decline in bradykinesia, which was confirmed by digital measures of progression. This informed internal company decision making to continue further clinical development of prasinezumab.

Regulatory challenges

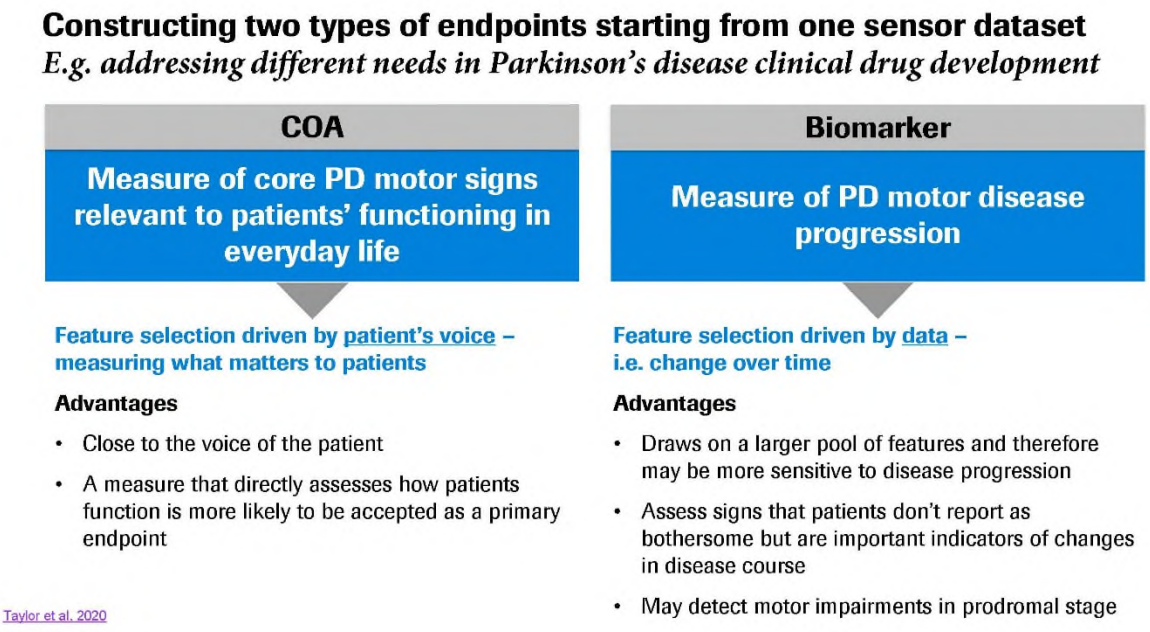
While companies are already leveraging digital technology for portfolio decision making, translating certain behavioural characteristics to reduced functioning remains a challenge for regulatory decision making and so the expectations of regulatory agencies are not yet aligned for digital endpoints. While the EMA has agreed that such behavioural characteristics are important, for example, the agency has accepted stride velocity 95th centile measured at the ankle (SV95C), which is captured by an ankle bracelet, as a secondary endpoint in Duchenne muscular dystrophy, the FDA has not accepted the MC10 gait analysis tool for Huntingdon's disease and Verily watch for PD.

Today's regulatory frameworks suggest constructing two types of digital endpoints from one sensor dataset; one endpoint that is data-driven while the other is patient-centric (see below) [3]. For example, for PD, the patient-centric endpoint would be a clinical outcome assessment (COA) of core PD motor signs relevant to patients' functioning in everyday life, which may be more likely to be accepted as a primary endpoint. The data-driven endpoint would be a biomarker measuring PD motor disease progression, which would draw on a larger pool of features and therefore may be more sensitive to

disease progression. This may also assess signs that patients do not report as bothersome, but which are important indicators of changes in disease course.

Summary

Digital consumer technology enables remote patient monitoring with many advantages, including higher measurement frequency, greater precision, greater accuracy, better reliability and more ecologically validity. The pharmaceutical industry is already leveraging digital technology for portfolio decision making, however, there are challenges for regulatory decision making and a lack of harmonisation on digital endpoints.



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Decentralised clinical trials

Lina AlJuburi, *Head, Regulatory Science and Policy, North America, Sanofi, USA*

Decentralised clinical trials are clinical investigations in which some or all trial related procedures and data acquisition take place at locations remote from the investigator. Decentralised clinical trials with medicinal products meet the patients, wherever they are, in a faster and more efficient process that benefits patients, healthcare professionals and industry.

Changing global environment

The COVID-19 pandemic has disrupted clinical operations and accelerated the adoption of decentralised trials. A survey reported in November 2020 showed that 76% industry respondents were running some decentralised trials but had concerns with data collection and quality [1]. Respondents were divided when asked about the clarity of current regulatory guidance on decentralised trials and data collection; 52% said yes, the guidance was clear, whereas 48% answered no. Surveys of clinical trial sites have also shown that patients had extremely or somewhat positive experiences with remote visits and that there is strong support for telemedicine going forward [2,3].

Learnings from decentralised trials

Sanofi has conducted several decentralised clinical trials over the last six years, with mixed outcomes (see below). Key to success has been integration of the patient voice and regulatory advice as well as alignment between the available technology and clinical development. It is also important to consider the healthcare ecosystem and disease area, for example, patients with a chronic disease tend to have good relationships with their healthcare providers so decentralised models can be disruptive and unfavourable. In addition, it is important to be aware of logistical issues for telemedicine between US states.

Sanofi's ambition is to have a hybrid trial model of remote and centralised monitoring, which is flexible for study and geographic requirements and offers patient-centric and site-centric options. This would facilitate opportunities to inform and respect patients, support clinical sites and engage countries globally. External collaborations will be key to facilitating improvements in data quality for decentralised data collection.

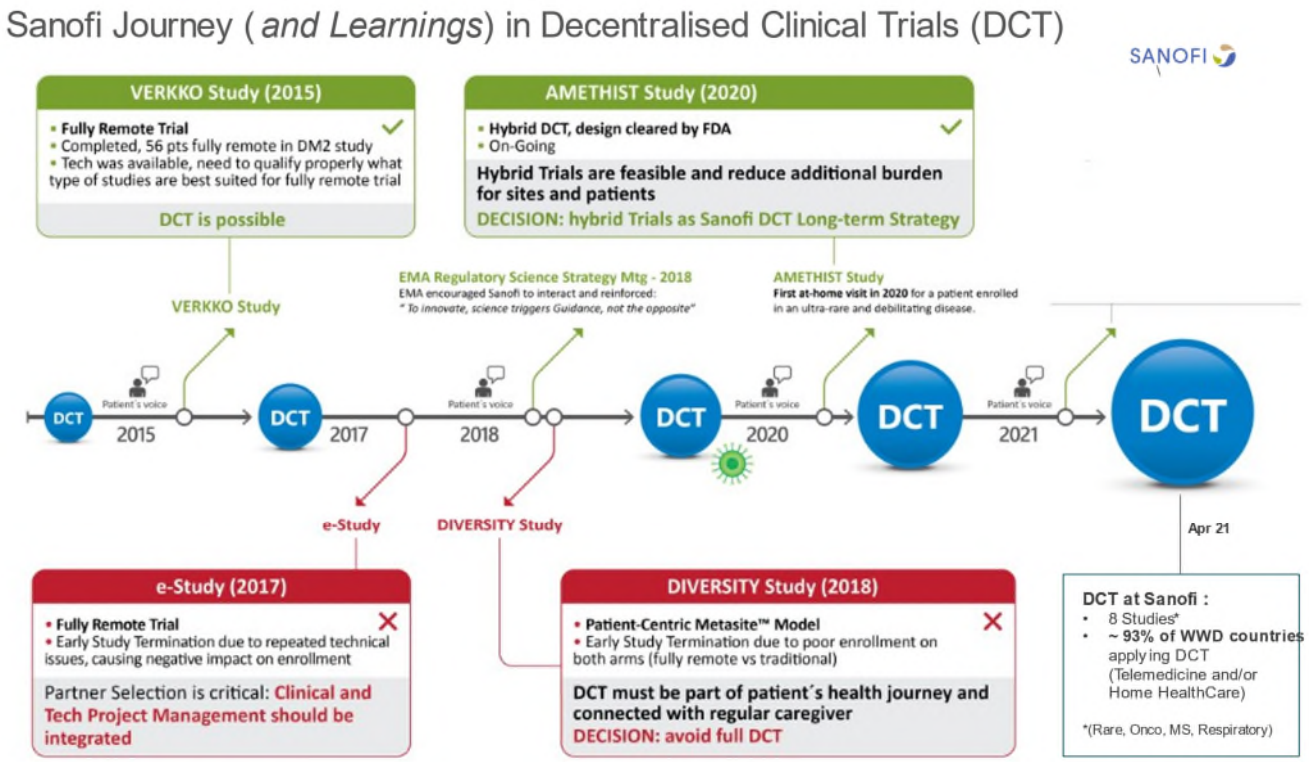
Regulatory guidance

The Danish Medicines Agency has produced the first guidance on the implementation of decentralised elements in clinical trials with medicinal products [4]. In addition to general considerations, the guidance covers recruitment; electronic informed consent; delivery of investigational medicinal products and self-administration at home; remote monitoring of trial participant safety; adverse event reporting; choice and validation of endpoints; remote access to source data; and IT systems as well as electronic collection, handling and storage of data.

The US FDA Oncology Center of Excellence has requested that applicants voluntarily add flags to datasets to discriminate between remote assessments and trial site assessments [5]. This will allow the FDA to learn from trials conducted in the COVID-19 pandemic that permitted some aspects of trial conduct to be performed remotely to reduce potential COVID-19 exposure. The FDA is expected to issue draft guidance on decentralised trials later in 2021.

Summary

Decentralised clinical trials do not necessarily mean that all trial-related procedures and data acquisition are taking place remotely; there can be a hybrid approach, which may be preferable as it facilitates options for different geographies, patients and trial sites. As well as patient centricity, confidence is key to success for decentralised trials; trial sites need to feel confident that the protocols and endpoint measurements are adequate without physical oversight and all stakeholders must be confident that the data is high quality, valid and traceable. Engagement with regulators is also critical and all stakeholders need to leverage the changing global environment (pre, during and post-pandemic).



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Digital technologies and an HTA evidence standards framework – what needs to be considered?

Mark Salmon, *Programme Director – Information Resources, NICE, UK*

Digital health is a large and busy marketplace, with innovation progressing at pace and real-world data (RWD) driving a revolution in evidence. There is huge potential and high system demand for digital solutions, which could help to optimise resources and alleviate the economic challenges that healthcare systems globally are facing. While the system roles of national agencies are evolving, the regulatory system is yet to align with this acceleration in digital health.

Since 2010, NICE has assessed over 50 technologies featuring a digital component through its diagnostics and medical technologies evaluation programmes, clinical guidelines, and other guidance products, such as Improving Access to Psychological Therapies (IAPT) digital therapies. NICE ran a digital health pilot in 2019/20, which provided learning for the methods and processes of the NICE Medical Technologies Evaluation Programme. In addition, NICE has recently launched an Office for Digital Health, a new team to help accelerate NICE's efforts to deliver innovation to the health and care system.

Evidence standards framework for digital health technologies

In recognition of the poor level of evidence coming from the digital health sector, NICE established an evidence standards framework for digital health technologies (DHT) in 2018, which has since been updated following stakeholder feedback. The framework provides not only a common set of standards for DHTs but also common principles and dialogue. It was developed in partnership with other health system partners and aligns with other standards for commissioning, interoperability, regulatory, technical/design and information governance.

The framework classifies different types of DHT by function, which then allows them to be stratified into three evidence tiers based on the potential risk to users (see below). The evidence level needed for each tier is proportionate to the potential risk to users from the DHTs in that tier. The evidence tiers specify evidence requirements including the types of accepted evidence, the minimum evidence standard and a best practice standard. The evidence tiers are cumulative therefore a DHT in the top tier (Tier C) must meet all the standards of the lower tiers (Tiers A and B).

Artificial intelligence and data-driven technologies

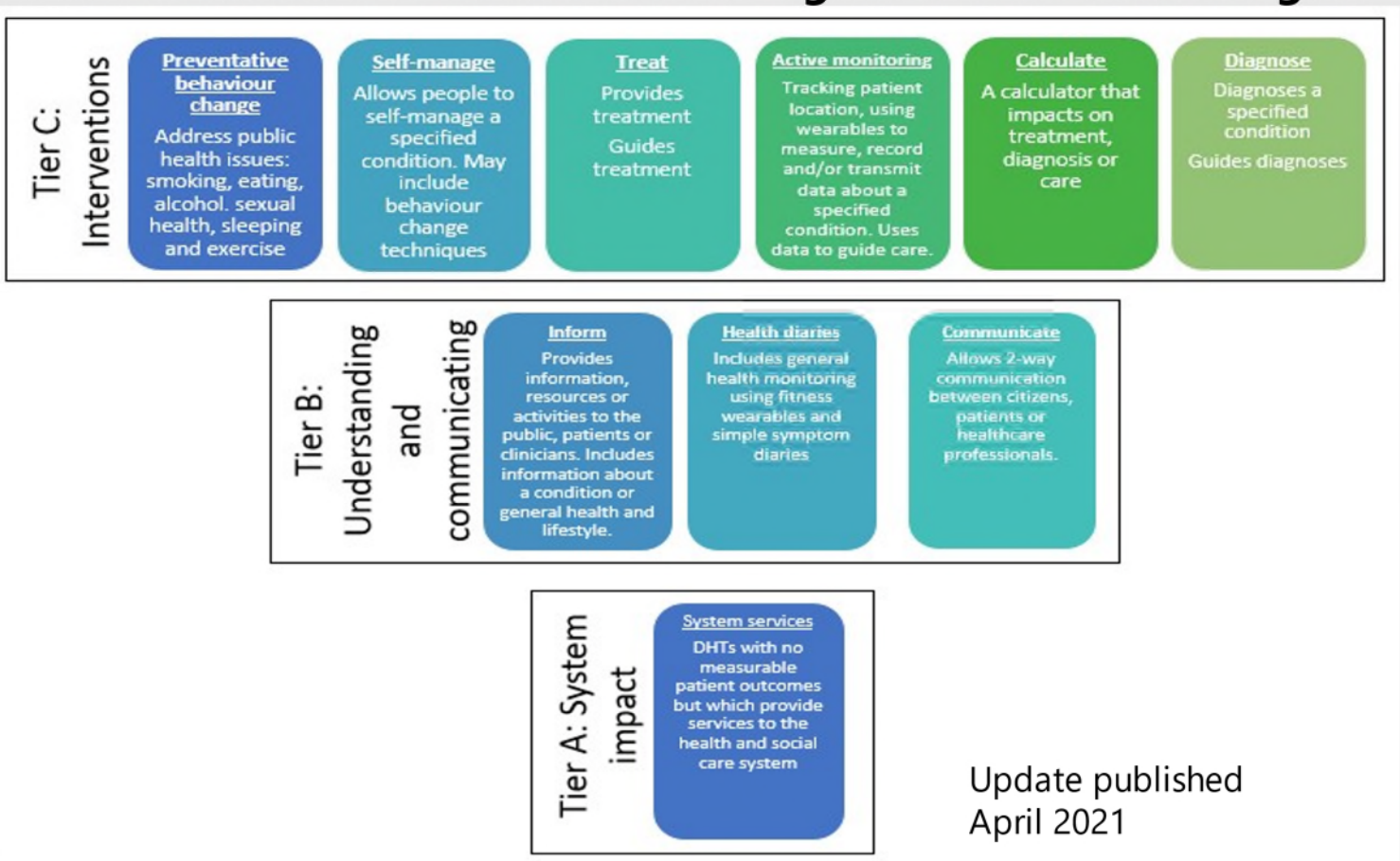
NICE is planning to update its evidence standards framework for DHTs in 2022 so that it fully incorporates data-driven technologies with embedded artificial intelligence (AI), including those that use adaptive algorithms. This will be carried out in collaboration with an academic AI partner as well as UK health system partners including the Medicines and Healthcare products Regulatory Agency (MHRA). There will be early consultations with industry and continuous iterative content working with stakeholders to ensure system fit.

A multi-agency advice service for AI and data-driven technologies is being launched in the UK, which will be jointly developed and delivered by NICE, the Care Quality Commission, Health Research Authority and MHRA. The service will cover regulation and HTA pathways for AI and other data-driven technologies and create a single source of information and advice for developers and adopters of these technologies.

Summary

To ensure confidence in the use of DHTs in health systems, it is important to have a standards-based benchmark for evidence requirements for HTA and other domains such as interoperability and regulation. Considerations for an HTA evidence standards framework for DHTs include a system wide multi-agency approach; industry and other healthcare system partner engagement; being responsive to change; alignment/conformity with international standards; and support for adoption for clinicians and patients.

NICE Evidence Standards Framework for Digital Health Technologies



NICE

Update published
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Global alignment or evidence standards frameworks for digital tools utilised in clinical development to generate evidence for regulatory decisions – would this be beneficial and what needs to be considered?

Regulatory viewpoint

Dr Florence Butlen-Ducuing, *Topic Lead in Psychiatry and Mental Health, Office of Therapies for Neurological and Psychiatric disorders, European Medicines Agency (EMA)*

Digital health technologies (DHTs) come in various forms and with different functions. Examples include sensors such as ingestibles and implantables; mobile health tools such as wearable devices for remote patient monitoring; digital biomarkers/endpoints; telehealth; digital record systems; health data analytics; and artificial intelligence/machine learning.

EU regulatory frameworks for digital health technologies

The EMA's remit is specific to DHT in the development, use or monitoring of medicinal products pre- or post-authorisation, with the aim to ensure safe and effective use and appropriate labelling. The DHT's development plan should comply with the general standards, guidelines and legal framework set for any medicine's development. A medical device must bear a Conformité Européenne (CE) mark to show that it conforms with the requirements of European directives and regulations.

The new **Medical Devices Regulation (MDR)** (EU 2017/745) came into application on 26th May 2021 after a four-year transition period. This changed the European legal framework for medical devices, introducing new responsibilities for EMA and national competent authorities in the assessment of certain categories of medical device. A Q&A document has been developed in collaboration with the Commission to provide practical considerations concerning the implementation of the MDR [1].

The **General Data Protection Regulation** (EU 2016/679) is a regulation in EU law on data protection and privacy in the EU and the European Economic Area, which came into force in May 2018. The assessment of data protection compliance falls outside of the scope of EMA; it is the remit of the national data protection authorities of Member States.

Software is being increasingly used for a variety of medical purposes, however, not all standalone software used within healthcare can be qualified as a medical device. **Medical Device Software** (MDSW) is defined as software to be used, alone or in combination with a medicine, for a purpose as specified in the definition of a 'medical device' in the MDR. For example, this could be in imaging assistance for diagnosis or treatment monitoring/adherence. The European Commission has produced an infographic outlining decision steps to assist qualification of MDSW [2].

The use of DHTs in clinical trials poses multiple challenges that require identification and input from different types of experts; early dialogue and a stepwise approach is key. Applicants can submit a qualification request at any time during development to receive qualification advice or a qualification opinion on the acceptability of their DHT [3].

EMA's experience of digital health technologies

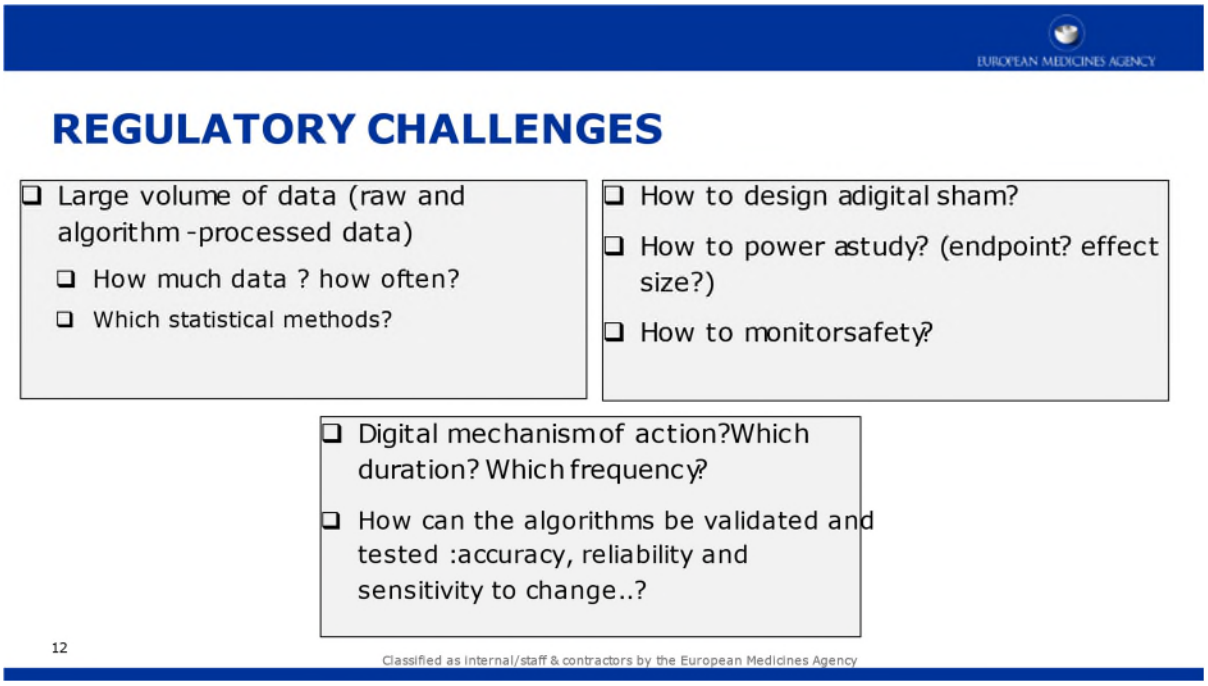
EMA's experience with DHTs so far has included marketing authorisation applications; variations; printed QR code/URL on package leaflets and outer cartons allowing patients/users/healthcare professionals to access dedicated websites containing the instructions for use; participation in digital-related Innovative Medicines Initiative (IMI) projects; and qualifications/Innovation Task Force meetings. The DHT

qualification procedure has experience with digital endpoints, digital biomarkers, digital measures, electronic clinical outcome assessments, eSource qualification, adherence/compliance. A qualification opinion has also been issued on stride velocity measured by an ankle wearable device, as a secondary endpoint for Duchenne muscular dystrophy.

Regulators are faced with several challenges to integrate data captured from DHT-based methodologies into benefit-risk assessment (see below). Large volumes of data (raw and algorithm-processed data) can be produced, and it is difficult to know how much data is required, how often it needs to be captured and which statistical methods to use. In addition, there are unanswered questions such as how to design a digital sham/placebo; how to power a study; how to monitor safety; how to define a digital mechanism of action; and how to validate and test algorithms?

Next steps

There are several DHT-related initiatives ongoing in Europe including the Heads of Medicines Agencies EMA Big Data Task Force, which had a workshop on artificial intelligence in April [4], the EMA Analytics Centre of Excellence and EMA Task Forces on Data Analytics and Digital Transformation. To move forward with regulatory frameworks for DHTs, it is important to have clear scope and definitions; a multidisciplinary approach; multi-stakeholder collaboration; a patient centred approach that facilitates trust; regulatory science to inform about applications in medicines development and evaluation; and a flexible/dynamic approach to reflect the fast-moving field of DHTs.



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Global alignment or evidence standards frameworks for digital tools utilised in clinical development to generate evidence for regulatory decisions – would this be beneficial and what needs to be considered?

Company perspective

David Isom, *Director, Regulatory Policy and Intelligence, Global Regulatory Affairs, Pfizer, USA*

Use of digital health technologies (DHTs) in development has accelerated advances in trial design, enabling decentralised models, digital endpoints and opportunities for novel placebo arms through real-world data. Modalities of decentralised clinical trials include telehealth; home health; sensors, wearables and apps; direct-to-patient drug delivery; and flexible sample collection.

Methods to assure validity of digital endpoints in clinical trials are evolving globally. NICE has been running digital health pilots and has developed an evidence standards framework for DHTs. The EMA has a qualification programme for digital technology-based methodologies to support approval of medicinal products. The FDA Digital Health Center of Excellence has recently been established to connect and build partnerships to accelerate digital health advancements; share knowledge to increase understanding and advance best practices; and innovate regulatory approaches to provide efficient and least burdensome oversight. The FDA-National Institute of Health Biomarker Working Group has developed the BEST (Biomarkers, EndpointS, and other Tools) Resource, which comprises a glossary to assist with common understanding and consistent use of terms [1].

There are many forums where companies are engaging with regulators and other stakeholders regarding the use of DHTs, such as the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), the Digital Medicine Society and the Innovative Medicines Initiative (IMI) (see below). In addition, companies are sharing learnings and experiences with each other through groups such as the Charles Group, a forum for executive regulatory leadership from companies.

In summary, DHT advances drug development opportunities, particularly in decentralised clinical trials and digital endpoints, and many forums globally are working to advance acceptance of these technologies, methods and clinical validation. However, there are regulatory challenges such as variability in guidance and uncertainty on requirements. Regulatory frameworks that promote global alignment of evidence standards will facilitate the use of digital technologies for evidence generation in clinical development. It will be essential to also take forward learnings from the COVID-19 pandemic, where regulatory flexibility helped to accelerate use of DHTs and companies shared non-competitive insights with each other as well as with regulators, and to optimise opportunities to promote global harmonisation through ICH.

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Digital health regulation – the view from the Asia-Pacific

Professor John Lim, *Executive Director, Duke-NUS Centre of Regulatory Excellence (CoRE), Singapore*

Digital health technologies have the potential to transform clinical development, lower trial costs and increase patient centricity. Although these technologies have implications for policy and regulation, current multi-stakeholder interest and the lack of legacy regulatory frameworks means there are opportunities for coordinated solutions.

Digital health regulation challenges

In November 2020, CoRE held a two-day virtual roundtable to discuss evolving issues in digital health regulation in the Asia-Pacific region [1]. On top of existing regulatory challenges in the region, digital health technologies were found to have unique complexities and conventional regulatory frameworks were deemed unsuitable to their fast evolving, iterative nature. Challenges identified through the discussions were the lack of data infrastructure, standards and interoperability; lack of system-level policies to facilitate data access, sharing and linkages across stakeholders and borders; limited awareness about and lack of standards for use of digital tools in clinical development; and inconsistent adoption of International Organisation for Standardisation (ISO) and International Medical Device Regulatory Forum (IMDRF) standards for software qualification and Software as a Medical Device (SaMD) classification.

Regulatory agility supports digital health implementation

During the pandemic, national regulatory authorities have facilitated access to essential COVID-19 health products through effective, agile regulation [2]. Regulatory agility refers to the adoption of risk-based, context-driven approaches and regulatory cooperation predicated on sound scientific evidence and information. It involves non-traditional approaches such as rolling submissions to ensure sound regulatory decision-making based on available data while not compromising safety, quality and efficacy. The term ‘agility’ is preferable to ‘flexibility’, which may connote unsafe cutting of corners.

Regulatory agility supports digital health implementation by increasing ability for faster adoption of digital health solutions and enabling earlier access to digital therapeutics and products for screening/diagnosis, tele-monitoring, and tele-treatment. In turn, digital health adoption enables greater regulatory agility; digital health solutions can advance clinical development and regulatory processes, and digitisation helps to overcome resource constraints and enhance processes and communication.

Regulatory convergence and reliance are key to facilitating regulatory agility and therefore the implementation of digital health technologies. There is a need for collaboration to develop international guidance on standards for using digital technologies in R&D and in the development of novel digital endpoints, as well as to accelerate convergence to internationally recognised standards such as those of the ISO and IMDRF. In addition, existing reliance models that Asia-Pacific countries participate in, such as the ACCESS Consortium, Project Orbis and the reliance pilot between Singaporean and Thai regulators, should be built upon.

Risk-based frameworks for digital health regulation

“Smart” regulation adopts fit-for-purpose approaches to ensure safety, quality and efficacy of digital health products without impeding innovation. Risk calibration identifies higher risk products and then adjusts the level and type of regulation accordingly. Early and frequent multi-stakeholder engagement is key to cultivating an agile development and regulatory environment. Risk-based frameworks for digital health

regulation that warrant further exploration include software precertification and the use of experimental 'sandboxes' for data and digital health.

Digital transformation in regulation

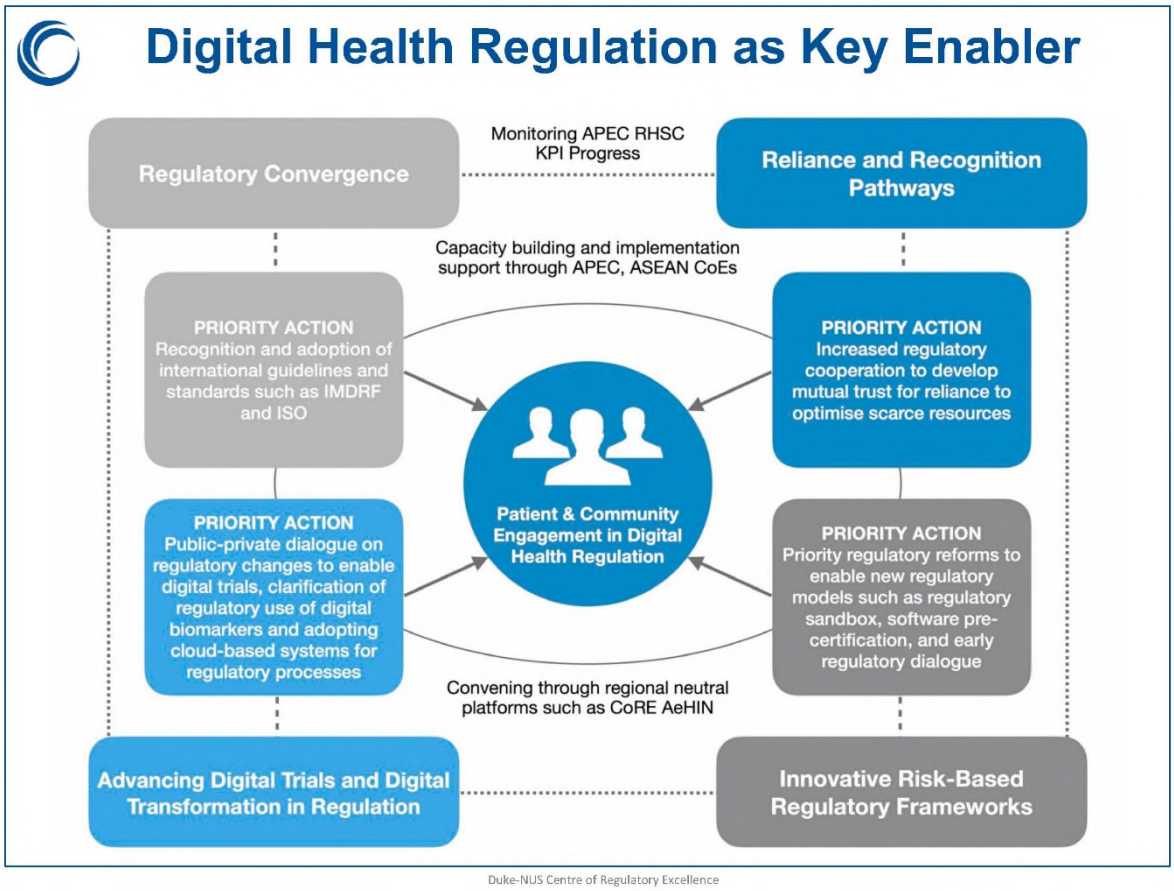
Data privacy, data security and cybersecurity issues must be addressed to allow the digital transformation of regulation. There is also a need to develop regulatory frameworks for the following purposes: use of digital technologies in clinical research and development, such as for digitally enabled trials, patient selection and recruitment, novel digital biomarkers or endpoints; data generation/collection (including real-world evidence) and remote monitoring; and leveraging artificial intelligence and machine learning.

Digital transformation of regulatory processes should be embraced to address the increasing amount of data and help to streamline processes. Examples from the pandemic such as the increased use of virtual inspections and electronic submissions should continue and cloud-based solutions like the Accumulus Synergy initiative should also be adopted.

Summary

Key elements to digital health regulatory innovation in the Asia-Pacific are patient and community engagement; regulatory convergence; reliance and recognition pathways; innovative risk-based frameworks; and advancing digital trials and digital transformation in regulation (see below) [1]. To advance digital health regulation in the region, the following recommendations should be implemented:

- **Promote regulatory cooperation, recognition and reliance** to facilitate timely access to health products and overcome resource limitations.
- **Employ neutral multistakeholder platforms** to advance discussion, sharing and adoption of digital health technology.
- **Increase capacity building and training** to improve competencies and abilities of regulatory professionals.
- **Promote public-private collaborations** to accelerate digital transformation of health products development and associated regulatory frameworks.



Asia-Pacific Economic Cooperation (APEC); Regulatory Harmonisation Steering Committee (RHSC); Association of Southeast Asian Nations (ASEAN); Centre of Excellence (CoE); Asia eHealth Information Network (AeHIN).

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Digital engagement of patients: how has its utilisation evolved to improve decision making and if so, in what way?

Patient perspective

Valentina Strammiello, *Head of Programmes, European Patients Forum (EPF)*

Patients expect digitalisation to facilitate self-management, person-centred care (as opposed to disease-centred care) and patient empowerment. They believe digitalisation will lead to improvements in care coordination, more effective treatments being developed, better outcomes and more effective and efficient health systems.

A survey conducted as part of the Chain of Trust project demonstrated that 92% of patients are willing to play a more active role in managing their own condition and 60% of patients who have never used telehealth would be willing to use it in the short-medium future [1]. Patients are generally comfortable and willing to share health data, especially if it is of vital importance to advance health research, help other patients, and ultimately benefit society. In terms of personalised care, over 65% of the survey respondents agreed that electronic health records can help them to receive care that matches better to their specific needs.

Issues in digital health

Key issues in digital health are late or no patient involvement, health literacy barriers, inadequate skills and competencies, lack of trust and lack of transparency in health systems. In addition, there are concerns around the affordability of digital tools; needs and impact assessments to evaluate added value; health inequalities and the diversity of voices involved; neglect of human factors; and whether the right outcomes are being measured.

The COVID-19 pandemic accelerated the deployment of digital health solutions and proved the importance of health data in managing cross-border health emergencies. However, it also highlighted some of the current shortcomings and issues such as scarce interoperability and lack of common health data definitions and frameworks; disparities in access to digital health; ad-hoc innovation approaches being used rather than systematic evaluation and implementation; concerns around the trust, data protection, privacy and accuracy of tracing apps; and the questionable use of data for research that could potentially have a significant impact on the health of many people.

Opportunities for patient involvement in digital health

Digital health is an emerging sector for HTA and is not yet well systematised. Digital health tools can collect data that inform HTA, but they would also benefit from undergoing their own HTA assessment to better understand their value. The speed at which the digital health sector is moving poses challenges for HTA bodies, who need to prioritise which technologies should be assessed. There is an opportunity for patients to add value to this priority setting by being involved in HTA horizon scanning activities.

There is also an opportunity with the new EU Medical Devices Regulation to identify where in the process of medical technology development should patient input be gathered. There could potentially be three stages of patient involvement: 1) clinical investigation/test, 2) conformity assessment (safety and performance), and 3) surveillance (post-market vigilance). All the information collected at these three stages could be equally valuable in the context of HTA.

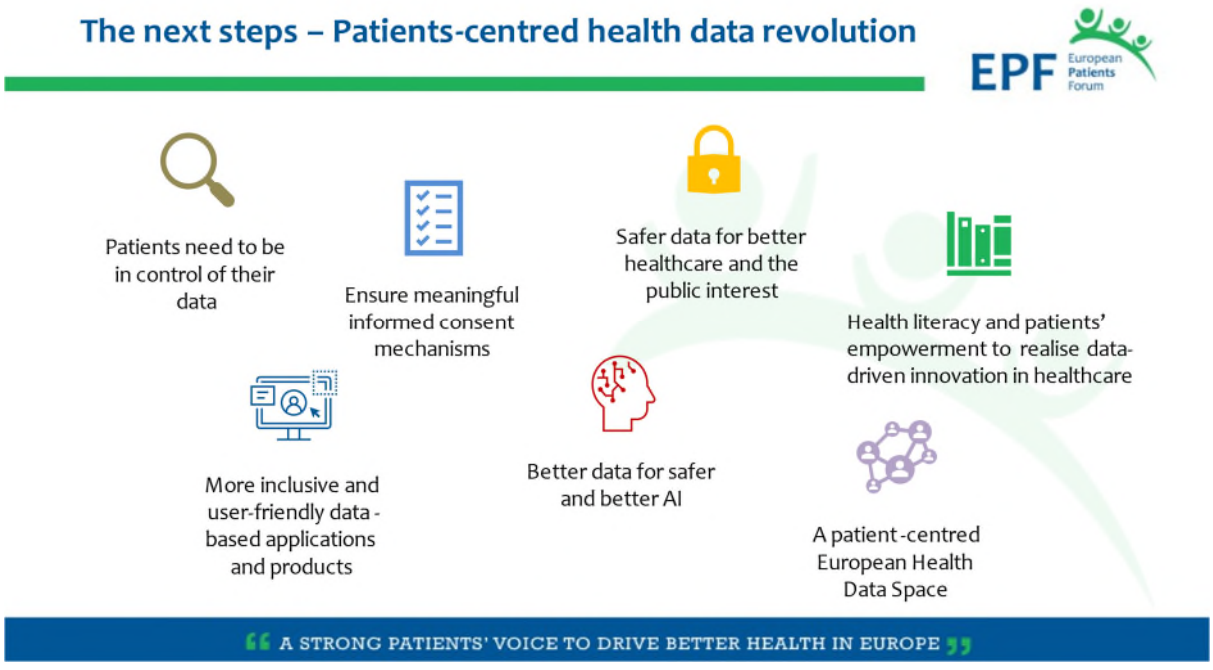
Next steps

EPF is aiming for a patient-centred health data revolution that will allow patients to be in control of their data (see below). There should be meaningful informed consent mechanisms; data that is kept secure; health literacy and patient empowerment; inclusive and user-friendly data-based applications and products; safe and effective artificial intelligence; and a patient-centred European health data space.

EPF is a partner in the Health Outcomes Observatory (H2O) project, which is setting up patient-centric pan-European and national data observatories with the aim of engaging patients and connecting providers. This will ultimately equip different stakeholders with the necessary data to improve patient care, for example, helping patient organisations to conduct evidence-based advocacy. The project will build a community of patient-centric and outcomes-driven organisations based on transparency and trust and will help to change mindsets and behaviours towards adoption of value-based health care and patient empowerment.

Summary

Patients' uptake of digital solutions relies on empowerment, health literacy and transparency and trust of health data governance. While there are challenges in the digital health space, evidence-based decision making is growing and there are opportunities for change in the 'post-COVID world' and with the enforced application of EU Medical Devices Regulation.



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Patient-focused drug development tools in a digital era

Digital engagement of patients: how has its utilisation evolved to improve decision making and if so, in what way?

Regulatory perspective

Dr Andrew Potter, *Mathematical Statistician, Office of Biostatistics, Division of Biometrics, US FDA Center for Drug Evaluation and Research*

Patients are uniquely positioned to inform regulators' understanding of the burden of disease and available treatment. Patients with serious chronic disease are experts on what it is like to live with their condition, but their 'chief complaints' may not be factored explicitly into drug development plans.

FDA's patient-focused drug development (PFDD) meetings elicit patient input to better inform the clinical context of benefit-risk assessment. Building on the experience of these meetings, FDA is developing a series of methodological guidance to enable stakeholders to go beyond powerful patient narratives and collect data that can serve as study endpoints and be used as evidence for regulatory decision making [1]. There will be four guidance documents in total that will focus on:

1. Collecting **comprehensive patient community input** on burden of disease and current therapy
2. Development of holistic **set of impacts most important to patients**
3. Identifying and developing **fit-for-purpose measures** for the identified set of impacts that can then be used in clinical trials
4. **Incorporating measures into endpoints** considered significantly robust for regulatory decision making.

Digital health technologies for patient-focused drug development

Digital health technologies (DHTs) have potential to generate rich and comprehensive information on how patients are functioning and feeling and help to minimise barriers to obtaining patient experience data during clinical investigations. DHTs can be operated and accessed remotely, can streamline study and data monitoring procedures, and can help maximise recruitment efforts among hard-to-reach patient populations. In addition, they can allow patients access to data about their health. Ultimately, DHTs may be used to assess study endpoint concepts that are meaningful to patients and can be used to evaluate clinical benefit.

Challenges of using digital health technologies

While there are clear advantages to using DHTs to generate patient experience data, there are a number of challenges including limited experience in aggregating and summarising data into a clinically meaningful endpoint. There are also methodological issues such as the definition of intensity and duration of activity, parameters for determining assessment periods in a day, minimal time requirements for device wearing during a day, aggregating data over numerous days and the risk of confounding the drug effect if patients are allowed to engage with their data.

Guidance on the use of digital health technologies

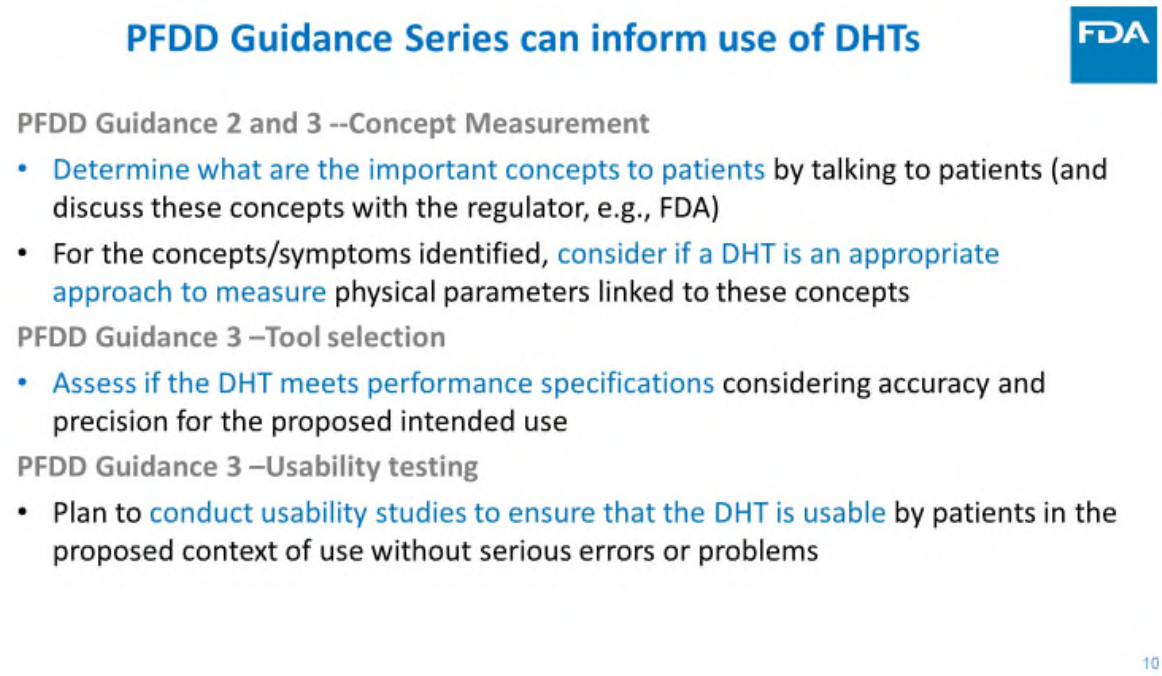
The PFDD guidance series can inform use of DHTs in terms of concept measurement (Guidance 2 and 3), tool selection (Guidance 3), usability testing (Guidance 3) and endpoint measurement (Guidance 4)

(see below). For example, DHTs may be considered an appropriate approach to measure physical parameters linked to important concepts/symptoms gathered from patients.

The Clinical Trial Transformation Initiative (CTTI) has developed recommendations and resources regarding use of DHT data to increase the quality and efficiency of clinical investigations [2]. However, further experience with the use of DHTs in clinical investigations is necessary. As with any proposed endpoint measure in a clinical investigation, it is recommended to seek frequent engagement with FDA early in the medical development process to discuss inclusion of DHTs in studies intended to support regulatory decision-making and labelling claims.

Summary

DHTs have promise but must be carefully considered prior to implementing in clinical trials. A DHT does not need to be better than traditional methods if it allows for more flexibility, for example remote vs. onsite participation. Important questions to consider are: can the DHT measure something we have not been able to measure before? Can the concepts measured be more easily and accurately assessed using a DHT? Will the DHT data truly complement data collected through traditional methods? Available resources and recommendations should be leveraged to determine the appropriateness of DHTs, and this should be discussed early and frequently with regulators.



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Digital engagement of patients: evolution and impact on decision making

Digital engagement of patients: how has its utilisation evolved to improve decision making and if so, in what way?

HTA agency perspective

Lindsay Lockhart, *Public Involvement Advisor, Scottish Medicines Consortium*

The experiences of patients, families and carers are a critical component of the Scottish Medicines Consortium (SMC)'s HTA process and decision making. Written submissions from patient groups provide patient and carer input into the assessment of medicines. These submissions describe what it is like to live with the condition the medicine may be used to treat and the impact that the medicine has/may have on the quality of life of patients and families/carers. Representatives from submitting patient groups can participate in the SMC committee meeting during which the medicine is discussed.

For medicines used to treat end of life and/or rare conditions, a Patient and Clinician Engagement (PACE) meeting may be requested by the submitting pharmaceutical company; PACE is an additional part of the SMC process that supports greater flexibility in decisions for these types of medicines and gives patient groups and clinicians a stronger voice in SMC decision making.

The SMC has a Public Involvement Network (PIN) Advisory Group made up of representatives from umbrella patient groups who have previous experience of submitting to SMC, together with SMC public partners, an SMC committee member who is clinical expert, and SMC staff. Group members use their knowledge and experience to inform and influence SMC strategy and processes for patient and public involvement.

Virtual patient engagement

Prior to the COVID-19 pandemic, only PACE meetings were held with virtual participation if required. The pandemic prompted SMC to adapt its ways of working and use virtual meeting technology for all its committee meetings. This change was facilitated through consultation and communication with stakeholders and developing a set of documents to help guide meeting participants. As part of the monitoring and evaluation process, feedback was sought on what went well and what could be improved.

Impact on decision making

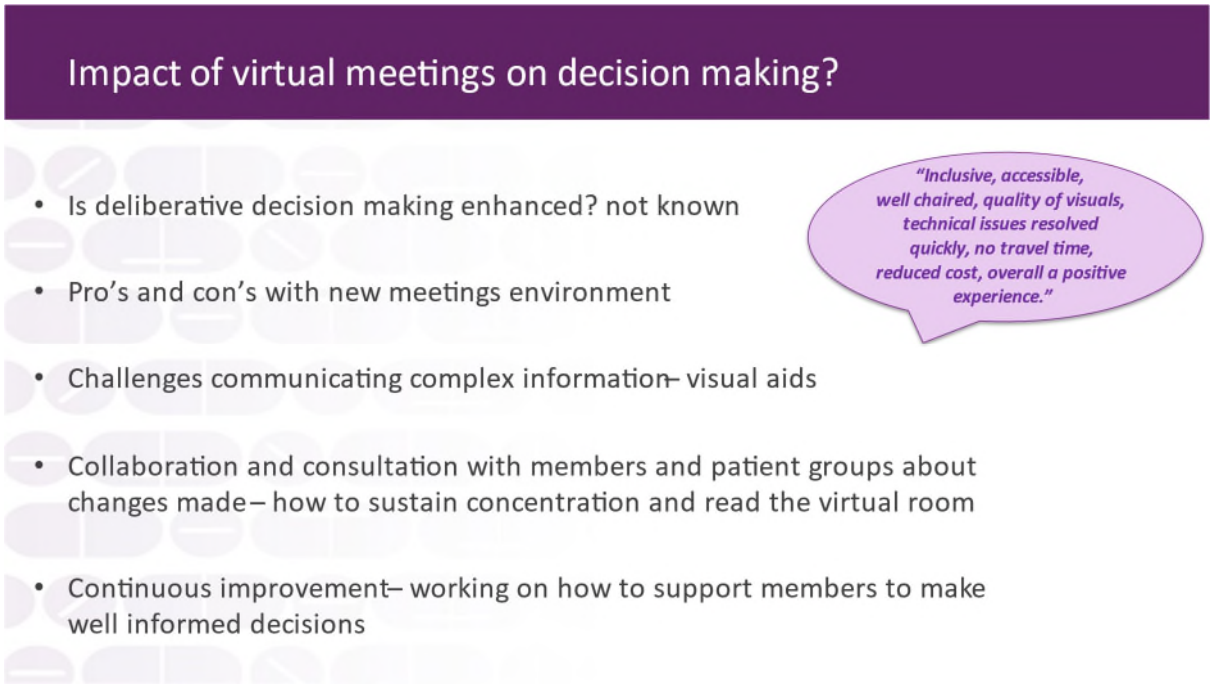
It is not currently known whether SMC's deliberative decision making has been enhanced by the shift to virtual meetings. The evaluation process showed that there were advantages to virtual meetings, such as improved inclusivity and accessibility, reduced cost and less travel time, as well as disadvantages, such as difficulties sustaining concentration and 'reading the room'. There were also challenges with communicating complex information virtually, highlighting the importance of good visual aids.

Continuous evaluation and improvement

The SMC is continuing to collaborate and consult with its stakeholders to evaluate its new virtual way of working and ensure they can actively participate in SMC meetings. To aid continuous improvement, hybrid meeting approaches and opportunities for networking and informal discussion will be explored.

Summary

The SMC involves patient group representatives in its submission processes, committee meetings and Public Involvement Network (PIN) Advisory Group. A new virtual meetings environment has been created due to the COVID-19 pandemic, which has advantages as well as disadvantages. Communication, collaboration and consultation with patient groups and committee members have been key to adapting to virtual meetings. Continuous evaluation and improvement will be important to ensure these stakeholders are supported to make well informed decisions.



Digital engagement of patients: how has its utilisation evolved to improve decision making and if so, in what way?

Company perspective

Robyn Carson, *Vice President, Patient-Centred Outcomes Research, AbbVie, USA*

Digital health technologies are becoming increasingly prominent in society, with many people now owning multiple devices that can connect with one another. This interconnectivity is creating a powerful network of devices where data can be shared. Analytical advances and artificial intelligence (AI) help to make sense of all this data, however, there are key considerations to ensure translation into meaningful outcomes. The accelerants behind this growth in digital health are awareness of patient centricity, which has been increasing over the last few years, as well as the ongoing COVID-19 pandemic.

Where are we with digital health today?

Increasing emphasis is being put on understanding the patient experience, for example, what it is like to live with a condition and the treatments associated with it. There is great potential to unlock this knowledge from social media, however, the most appropriate and compliant way to do this needs to be identified. Careful consideration must be given to the choice of social media platform as well as the analytics used to ensure that meaningful data can be separated from surrounding noise.

Digital technologies are being used to efficiently operationalise public health programmes. They can provide a seamless patient experience, map the patient journey, reduce administration costs, and support informed patient decision making. For example, mobile apps for COVID-19 vaccination programmes have been developed that allow users to register for their vaccination, check into their appointment, access their vaccination record and share their experience on social media.

Digital technology can play a role in decision making about patient health, from how to diagnose earlier to how to better monitor outcomes of treatment. For example, in Parkinson's disease, AI has been applied to administrative claims data to identify individuals with a high probability of eventually being diagnosed with the disease [1]. The Pursuing Real-world Outcomes via Duopa Ecosystem (PROviDE) study has also monitored motor symptom improvement of patients with Parkinson's using wearables that support passive continuous data collection [2].

Where can digital go from here?

A key focus for the pharmaceutical industry is using digital technologies to globalise clinical trials. This will help to diversify clinical trials, facilitate patient mapping, aid patient recruitment and engagement. Exploration of virtual reality and gamification may also highlight new ways to help patients, from therapy to engagement. Telemedicine such as AI-supported 'chat bots' may be accelerated to facilitate 24/7 information exchange, which could be supplemented with virtual physician appointments. Partnerships will be key to advancing these technologies in a patient-centric manner.

Challenges and considerations

There are challenges that need to be addressed to realise the full potential of digital health technologies. These relate to data privacy/security; data misuse; social media; patient diagnosis e.g. trust of self-reported data; and analysis and interpretation methods. There is also a question around the 'right' context in which to use digital health technologies i.e. just because something can be done digitally, should it

always be done that way? It may be possible to develop a framework-based assessment to guide the choice of inclusion of digital health-enabled outcomes in a clinical trial (see below).

Summary

Digital health technologies can help to improve understanding of the patient experience, efficiently operationalise public health programs and support diversity in clinical trials. Contextualisation of data is key, and patients must be involved rather than making assumptions about their experience. The pharmaceutical industry plays an important role in turning data into something meaningful for decision making and must partner with other stakeholders to unlock the full potential of digital health technologies.

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"Dynamic dossier" cloud-based approach for submission of data to regulator and HTA agencies - what is the ROI for companies and agencies?

Company perspective

David Dorsey, *Director, Global Regulatory Policy and Intelligence, Janssen, USA*

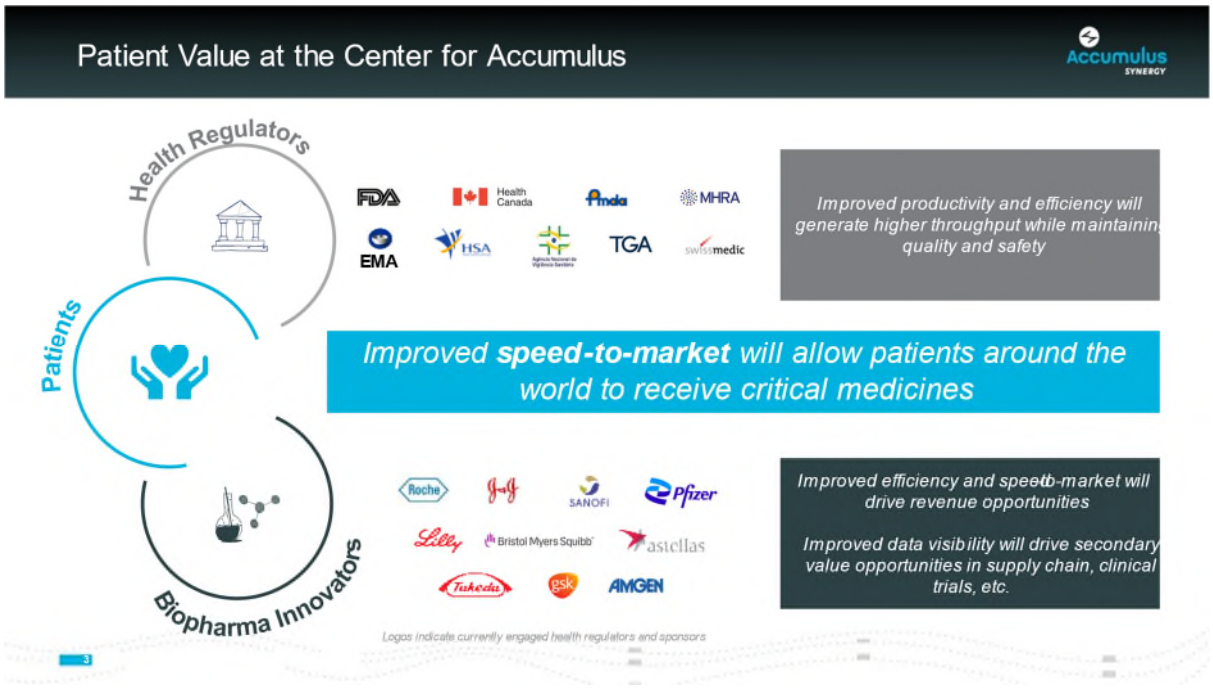
Challenges to the pharmaceutical sector today include escalating development costs, keeping pace with medical innovation, increasing complexity of data and evidence, enabling global collaboration and addressing access and availability concerns. These challenges are not helped by the unnecessary complexity and inefficiency in data exchange between sponsors and regulators, such as locked datasets, manual processes, and reliance on narrative and textual elements. Both stakeholders recognise that these existing ways of working can be improved.

Accumulus Synergy is a non-profit company working to transform the regulatory submission process by creating the first-ever global dynamic data exchange platform. This will change regulatory submissions from the traditional dispatch of static information and documents to a cloud environment with real time data and communication.

The Accumulus cloud platform will be made up of secure sponsor-only and regulator-only spaces, as well as a shared space where information can be exchanged, and collaboration occurs. An underpinning prerequisite is the security, privacy, and protection of patient information and confidential company information. The current focus is the exchange of data related to regulatory submissions i.e. between sponsors and regulators and from regulator to regulator. Current uses and releases focus on collaboration and more efficient use of data for late-stage regulatory submissions. In the long term, the benefits unlocked by Accumulus will apply to the entire research and development spectrum, including post-approval lifecycle management.

Accumulus Synergy seeks to transform global regulatory engagement and collaboration. Since inception, Accumulus Synergy has worked to partner and collaborate with global regulators to co-create solutions that will ensure regulatory convergence. Several global regulators and large pharmaceutical companies are currently engaged with Accumulus (see below).

For sponsors, the return on investment (ROI) of the Accumulus platform will be improved productivity and efficiency, which will generate higher throughput while maintaining quality and safety; improved efficiency and speed-to-market will drive revenue opportunities, and improved data visibility will drive secondary value opportunities in supply chain, clinical trials etc. For regulators, the ROI lies in in the creation of new opportunities for more efficient engagement with fellow regulators, sponsors, and others. Nonetheless, the overarching ROI of Accumulus will be in value to patients, as improved speed-to-market will allow patients around the world to receive critical medicines and improved use of data will provide for enriched and more real-time regulatory decisions to enhance patient use of therapeutics and vaccines.



Enabling the digital ecosystem to transform quality data and clinical insights into evidence for improved patient outcomes – what needs to be considered?

Company perspective

Dr Virginia Acha, *Global Lead, Global Regulatory Policy, MSD*

To build 'intelligent' healthcare and regulation, decision making must be supported by digitally available data and enhanced by data processing, analytics, machine learning and artificial intelligence (AI). This requires mechanisms for bringing together a set of parties to interact online i.e. via digital platforms. Intermediaries and infrastructures need to be positioned to record and extract all data related to online actions and interactions among users of the platform.

Adoption of digital practices

Medicines regulation has been slow to adopt digital practices, which may be because it faces greater, but not insurmountable, barriers and risks compared to other sectors. Adoption of digital practices requires organisational capabilities as well as willingness and commitment at all levels of the organisation. Beyond the organisation, there needs to be system requirements for coordination and acceptance, common standards, and platforms.

Challenges to transform data into evidence

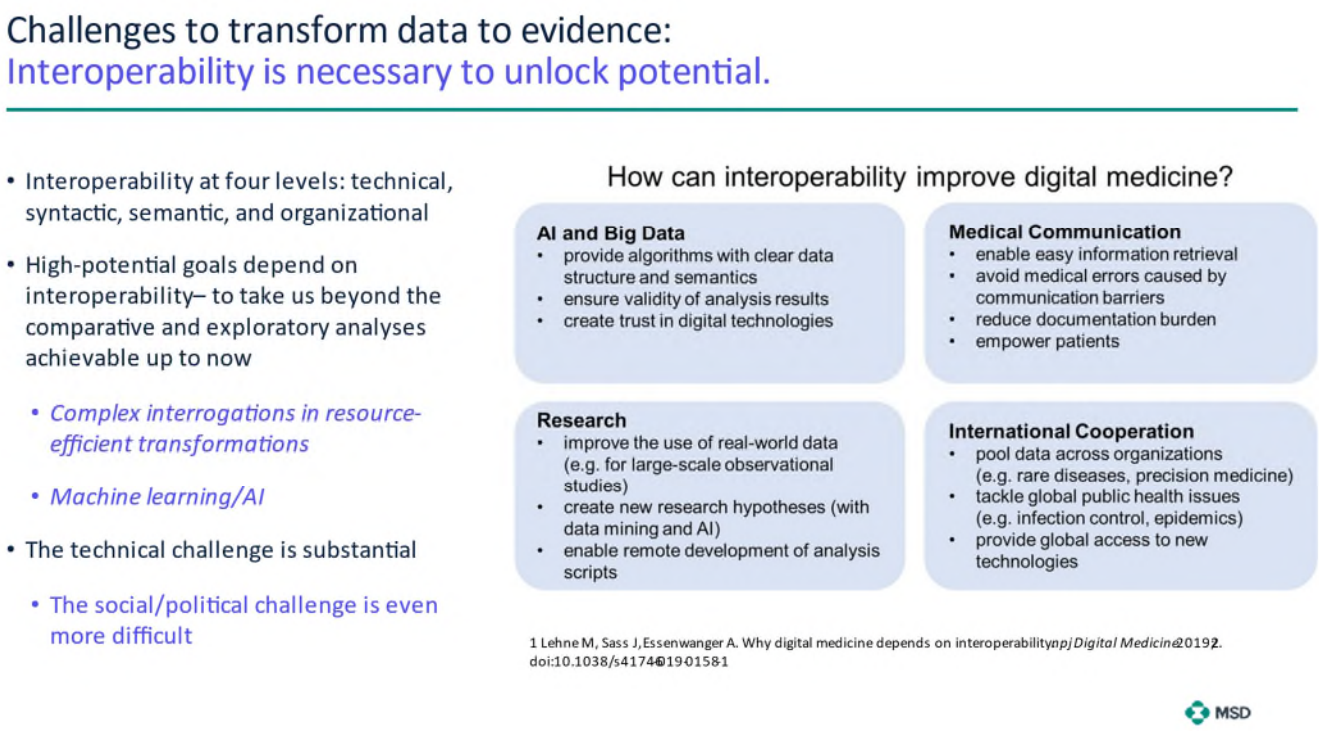
Data needs to be fit for the purpose planned. The research question, not the data itself, allows the quality of 'evidence' and research design should define the nature of the data sought. There are challenges in being able to identify the data (data discoverability) and to have access, as well as the relative risk of false findings, particularly when data is being repurposed.

Data quality is concerned with accuracy, validity, consistency, replicability, and transparency. However, the current lack of standards means it is difficult to define data quality. Efforts are underway around the world to establish data standards, for example, the European Medicines Agency (EMA) has launched an initiative to develop a data standards strategy; it will be important to ensure harmonisation of these global efforts. In addition to data itself, data processing and analytical methods also need to be fit for purpose, validated, replicable and transparent.

Interoperability is necessary to unlock the potential in transforming data to evidence. This includes interoperability at all four levels: technical (data exchange capability), syntactic (data format and structure), semantic (language and terminologies), and organisational level (policies and workflows)[1]. This will take us beyond the comparative and exploratory analyses achievable up to now and enable complex interrogations in resource-efficient transformations. While the technical challenge is substantial, the social and political challenge is even more difficult.

Summary

Advancing digitally sourced and digitally transformed data to generate high quality evidence will happen but maybe not as quickly as expected. To adapt, the regulatory discipline must have willingness/commitment, organisational capabilities and common standards and platforms. The challenges to transform data to evidence are around research design and fit-for-purpose data; data quality and standards; and interoperability. To overcome these challenges, there must be coordination and alignment internationally and across stakeholders, confidence-building measures and a learning focus where positive and negative experiences are shared.



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Section 3: Breakout discussions

Breakout discussion A

Utilisation of digital tools for evidence generation in clinical development to improve regulatory/HTA decision making – what is needed to ensure they are regulatory/HTA grade?	
Chair	**Professor Hans-Georg Eichler,** *Department of Clinical Pharmacology, Medical University of Vienna, Austria*
Rapporteur	**Megan Doyle,** *Policy Director, Global Regulatory & R&D Policy, Amgen, USA*

Background

Digitisation and digital health technologies are transforming clinical development and companies, regulators, and Health Technology Assessment (HTA) agencies are looking to derive actionable insights from the data being generated. This is providing potential opportunities across medicines research and development, review and reimbursement as well as in the post-approval space. Digital technologies can facilitate a better understanding of both the safety and effectiveness of medicines by generating insights on patient behaviours and care outcomes, either as part of clinical development process or in real-life settings. In the development space, they have enabled innovative trial designs to be considered through the utilisation of apps, wearables and digital biomarkers.

These digital opportunities have been accelerated by the ongoing pandemic, underpinning not only the conduct of clinical development but also data generation. Digital health technologies have the potential to change how companies, regulators, HTAs and patients monitor, manage, predict, and make decisions about healthcare.

The key challenge for use in clinical development is how to ensure digital technologies can provide regulatory and HTA grade outcomes, as well as how its continuous evolution should be regulated. Indeed, what has been identified previously as regulatory challenges included inconsistency in digital practices; qualification, guidance, and expertise to accommodate rate of change to technological innovation; issues with data validity/integrity and security; and the ability of trial sites and investigators to utilise digital tools.

The aim of this breakout is to discuss the main areas where digital tools are being used in clinical development to generate evidence that can be utilised in review and reimbursement decisions, what is needed to ensure that the evidence generated is regulatory/HTA grade, and how this can improve decision making. This breakout was therefore asked to build on the workshop discussions, with the following objectives:

- **Identify the main areas/opportunities that digital tools are being used in clinical development** to generate evidence for regulatory and HTA decision making - what is working, could improve or hasn't been tried yet?
- **What are the current or perceived challenges** to ensure that evidence generated is regulatory and/or HTA grade - what are the key areas of concern?
- **What needs to be considered to support the evolution of digital tools** so that they reach their potential to provide regulatory/HTA grade evidence?
- **What policy/research is needed** to address the key challenges?

Discussion results

Q1. Identify the areas/opportunities that digital tools are being used in clinical development to generate evidence for regulatory and HTA decision making - how acceptable is it for regulatory and HTA decision making? What is working well (routinely accepted), could improve (not routinely accepted) or has not been tested yet (too early)?

Q2a. What are the biggest challenges (real or perceived) to ensuring that the data generated by the digital tools are regulatory/HTA grade for use in review and reimbursement decisions?

Q2b. What needs to be considered to support the evolution of these digital tools to ensure they reach their potential to provide regulatory/HTA grade evidence?

Key challenges (Q2a)	Considerations (Q2b)
Regulatory/HTA coordination of standards and sponsor planning for regulatory and HTA expectations	Need for a tripartite consortium of sponsors, regulators and HTA to discuss frameworks and standards
Conservatism from both sponsors and regulators towards digital tools • Still measuring against older, outdated measures • Consistently requiring comparison to existing endpoints rather than treating them as new endpoints	Addressing conservativism: • Regulator input on study design and finalised protocols - use early interactions at the design phase • Make use of COVID-19 experience and lessons learned from both sponsor and regulator perspective – what really was at risk and what was not
Qualification programmes to validate digital tools • More accessible to larger sponsors/consortia • Technology is moving quickly so need to avoid duplication and gain insights about existing frameworks for individual sponsors to follow • Need to define 'fit for purpose'	• Interactions with regulators are key – they are receptive to novel approaches • Early interactions with regulators during design phase - more dialogue • Identify examples of what is fit for purpose - over time can arrive at expanded frameworks
Payers/HTA scepticism of Patient Reported Outcomes (PROs) • PROs are not necessarily patient relevant • Assumptions can be misleading – is something relevant to the patient if they do not complain about it? • Digital tool may capture this information more easily • Can PROs and digital tools be disaggregated?	Data utility for performance-based agreements • What would be of value to payers to overcome scepticism? • PROs need relevant difference or relevant effect to translate the benefit into something tangible • Validate or triangulate the data – response of the individual vs. way data is collected • Use digital tools for less subjective measurements • Ask the patient (patient reported is not the same as patient relevant), then determine best way to measure
Dealing with **voluminous data/noise** • How to distinguish the realities from the background noise • How to analyse potential missing data e.g. user takes off a wearable	Work with broader community of stakeholders (outside healthcare) to leverage techniques/approaches from other sectors • E.g. Natural Language Processing (NLP) to create structured dataset from narrative/unstructured data
Potential to **exacerbate digital divide** • Decentralisation has opportunity to reduce disparities in trial access • But if areas are remote, may still have disparities	• Invest in infrastructure to reduce the impact • Address misconceptions that you need 100% connectivity/device access to participate • Show examples of how these challenges have been addressed/overcome

Q3. Focusing on 1-2 key challenges from Q2a, what could be potential solutions or policy/research projects that could help to address these challenges?

Key challenge	Solution or policy changes required
Conservatism/ scepticism towards digital tools	• Publication of case studies to demonstrate validity of new endpoints measured with digital tools • Promote mindset that these endpoints should be treated as new, rather than comparing to outdated flawed endpoints • Encourage more parties to engage in qualification programmes to develop new endpoints – requires de-risking (there may be other acceptable methods to get the product developed), determining which data source has more fidelity and assess accuracy • Interest/utilisation may just be driven by recognition that continuous data from a digital tool is likely to be more robust • Need to develop life cycle approach to regulation/HTA assessment as current approach leads to conservatism for sponsors (since changing endpoints can raise challenges from HTA bodies) • Work with clinicians, patient communities and pharma companies on disease registries could be a good example of a collaborative approach for these endpoints
Lack of regulatory/HTA standards	Good guidance from regulators in the biomarker space and on how to capture patient voice (Clinical Outcome Assessment guidance) but there is a need for **guidance for digitally derived endpoints** that do not fit into these categories.

Q4. Recommend future research projects for CIRS and other groups to undertake in this area – what should be considered to support or improve current activities?

1. Engage with stakeholders to coordinate a way forward, building on discussions from this workshop:
    - Surveys of companies for case studies
    - Surveys of what digital tools have already been successfully used in the past 3-4 years
    - Identify via research/publications what validated endpoints for digital technologies exist.
2. Coordinate interactions on the development of standards across HTA bodies and regulators.
3. Engage patient groups to see what is relevant to them in various therapeutic areas.

Breakout discussion B

Development of a globally aligned digital practice framework for utilisation of digital tools in clinical development – what value would it seek to provide?	
Chair	**Dr Nick Crabb,** *Programme Director, Scientific Affairs, NICE, UK*
Rapporteur	**Lesley Maloney,** *Product Development, International Regulatory Policy – Digital Health, Genentech/Roche, USA*

Background

As regulatory and HTA agencies adapt to the use of digital technology in clinical development, how aligned are their requirements within and across jurisdictions? What are the opportunities for both stakeholders post-pandemic to ensure the power of digital technology can meet its potential in the development, review and reimbursement space? These are important questions to consider, as data generated in one jurisdiction for the purposes of one stakeholder needs to be utilised for decision making either by another stakeholder in the same jurisdiction (e.g. regulatory and HTA) or in another jurisdiction. There needs to be standards that can give confidence to regulators and HTA in the jurisdiction where the data is not generated, as well as to provide a framework for new entrants into the space who come from a technology background but do not necessarily have experience within pharmaceutical development and vice versa.

The aim of this breakout is to discuss why the development of a globally aligned digital practice framework for utilisation of digital tools in clinical development would provide value. The breakout group was asked to build on the workshop discussion of this topic, with the following objectives:

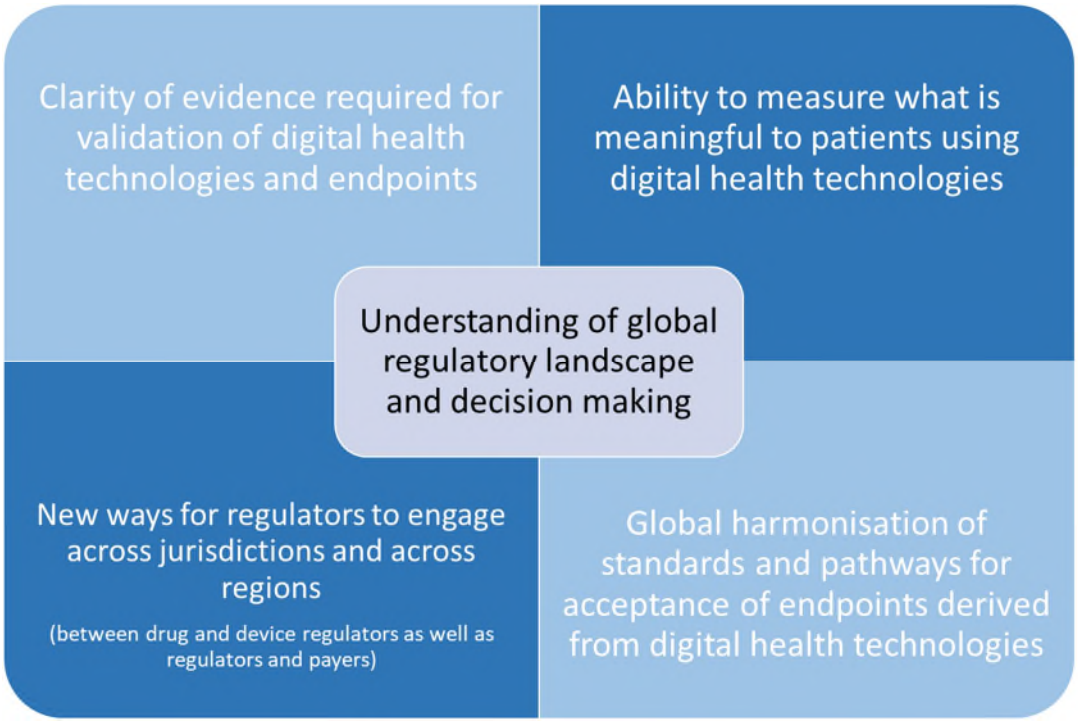
- **Assess the need for a globally aligned digital practice framework** - why would this be of value to develop?
- **Identify the key characteristics/domains that would need to be considered** within such a digital practice framework - what are the building blocks for the development of an effective framework?
- **Evaluate the challenges and make recommendations regarding solutions and potential policy actions needed** - what should be considered to support the evolvement of a digital practice framework?

Discussion results

Q1. What is the value of a globally aligned digital framework?

The breakout group concluded that a globally aligned digital framework reduces inefficiencies in R&D and supports efforts to engage a greater variety of patients in drug development efforts. Use of digital technologies in drug development allows for more innovative trials that better reflect the patient voice and patients' lived experience. This supports the end goal of delivering personalised healthcare and improved patient outcomes at a reduced cost to society.

Q2. Identify the key characteristics/domains that would need to be considered within such a digital framework.



Q3. What should be considered to support the evolvement of a globally aligned digital practice framework? Evaluate the key perceived challenges and make recommendations on potential solutions and policy actions needed.

Key challenges	Potential solutions
Lack of clarity around evidentiary requirements from regulators for the tool as well as the endpoint. **Lack of global alignment on requirements**, so re-validation or re-qualification potentially needed within each jurisdiction.	• Establish global standards for the analytical validation of the digital health technology/device • Establish global standards for the clinical validation of the endpoint (Clinical Outcome Assessment or biomarker) derived from the digital health technology • Promote regulatory reliance on digital health technology acceptance/qualification or consideration of work sharing model like Project Orbis • Identify building blocks needed for development and acceptance of digital health technologies - begin with Digital Medicine Society (DiME) checklists but need to go deeper • Consider reflection paper by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and/or joint papers between ICH and International Medical Device Regulators Forum (IMDRF)
Lack of ways to engage with regulators and make decisions on digital tools in a timely manner that keeps pace with innovation	• More agile processes for verification and validation of digital tools • More fit-for-purpose qualification pathways
Variety of initiatives, influencers and decision makers in the digital space that can lead to confusion as well as lack of prioritisation	• Conduct maturity model assessment or landscape analysis
Data quality issues, which could limit the ability to transform generated data into evidence	• Build on existing mechanisms such as those used for real-world data to ensure data quality
Overlaps between clinical, technology and healthcare mean **new collaboration models are needed** e.g. between drug and device regulators regarding advice	• Revise frameworks/mechanisms to support greater interaction between drug/device regulators and ensure greater coordination and feedback to sponsors • Consider inter-agency models (e.g. UK collaboration between MHRA and NICE)
Difficulty determining what is meaningful to patients, including in comparison to endpoints that are currently used. This could also create issues for HTA agencies doing comparative-effectiveness between 'new' and 'old' endpoints.	• Invite stakeholders to engage in discussing meaning of new measures as compared to traditional/gold standard • Continued education and awareness building with HTA agencies around use of digital health in generating evidence for clinical development/regulatory decision making
Concern around **proliferation of individual company endpoints** rather than work through pre-competitive consortiums	• Build upon work started by DiME to drive collaboration between sponsors, regulators, patients and clinicians in development and improve acceptance of endpoints derived from digital health technologies

Digital technologies: enabling evidence generation in clinical development; 24-25th June 2021	
Digital tool cleared/approved as a device does not necessarily mean it is fit for purpose for use a digital endpoint	*Due to limited time, solutions were not suggested for these challenges so further consideration may be needed.*
Need for global alignment on terminology e.g. digital endpoint, digital biomarker, digital drug development tool	
Lack of clarity for acceptance or requirements for core/platform endpoints	

Q4. Recommend future research projects for CIRS and other groups to undertake in this area – what should be considered to support or improve current activities?

1. Conduct a landscape analysis/maturity model assessment for digital health, with specific emphasis on use of digital health technologies to develop endpoints for use in drug development and in regulatory decision making.
2. Encourage development of global workstreams on digital practice frameworks, whether through ICH or other means, to align terminology, validation requirements and globally harmonised pathways and approaches.

Breakout discussion C

How can common digital infrastructure and platforms for collaboration and work sharing during review/reimbursement and post-approval be facilitated – what is needed within the digital ecosystem?	
Chair	**Fabio Bisordi,** *Global Head International Regulatory Policy, F. Hoffmann-La Roche Ltd, Switzerland*
Rapporteur	**Dr Ryan Hoshi,** *Director, Regulatory Policy and Intelligence, AbbVie, USA*

Background

At a CIRS workshop in December 2020 there was agreement that the use of digital technologies accelerated during the pandemic needs to be retained post-pandemic, particularly around a "Common digital infrastructure and platforms for collaboration and work-sharing during the review, including cloud submissions". Importantly, this could have impact on ease of submission and review, opportunities for parallel review, facilitation of regulatory processes, reduction of duplication, improved review efficiency, potential for increased harmonisation and alignment, and accelerated regulatory approval and patient access.

The idea of a dynamic centralised dossier is not new; with the use of new digital technologies, an ecosystem where regulators can access emerging data on a therapeutic across the product lifecycle (i.e. safety, efficacy, quality) in real time, within a shared dynamic, cloud-based environment, is becoming a reality. This is particularly enabled through groups like the Accumulus Synergy, which is a first-of-its-kind global collaboration between industry and regulators to provide a platform for real time information sharing. A common digital platform can have several benefits, some of which are outlined above, as well as other potential aspirations such as facilitating worksharing and reliance, or a parallel review between regulatory and HTA.

Nevertheless, a number of challenges remain, also initially discussed at previous CIRS workshops, which include inconsistency in digital practices; qualification, guidance, and expertise to accommodate rate of change to technological innovation; issues with data validity/integrity and security. Questions remain on how aligned these systems could be across jurisdictions and what else is needed in terms of policies/tools and research to ensure the power of digital technology can meet its potential in the development, review and reimbursement space.

The objectives of this breakout were to discuss:

- **What are the main goals** for having a common digital infrastructure and platforms for collaboration and work sharing during review/reimbursement and post-approval?
- **What are the key challenges** to ensure an efficient and effective digital ecosystem through a common digital infrastructure?
- **What policies/tools or other research is still needed** to make common digital infrastructure and platforms for collaboration a reality?

Discussion results

Q1. What are the main goals for having a common digital infrastructure and platforms for collaboration and work sharing during review/reimbursement and post-approval?

The breakout group agreed that a common digital infrastructure would be helpful for promoting **regulatory reliance,** for example**,** to **verify products** and information for regulators relying on reference authority decisions. The WHO collaborative registration procedure uses a common data platform to share information from dossiers to individual member states. However, confidentiality agreements can limit access to the data and direct work with reference authorities outside of the WHO process can be challenging. A common digital infrastructure would also help to **improve data accessibility, enable collaboration and increase harmonisation** e.g. establish a common terminology for digital health technologies, and ultimately **accelerate patient access.**

The group agreed that the overarching goals of a common digital infrastructure are to enable:

- **Trust and transparency**
- **Access to the same data at the same time**, enhancing collaboration and allowing for simultaneous submission and review
- **Collaboration and data analysis** – an example case study from the real-world data (RWD) perspective is the European Health Data & Evidence Network (EHDEN).

Q2. What are the key challenges to ensure an efficient and effective digital ecosystem through a common digital infrastructure?

Q3. Recommend future research projects for CIRS and other groups to undertake in this area – what should be considered to support or improve current activities?

1. Benchmarking or landscaping analysis of current policies and regulations regarding the use of digital infrastructure e.g. use of digital health technology, data policy, data security, data privacy. Existing benchmarking studies and learnings from other fields/industries should be leveraged to develop best practices.
2. Additional workshops on related or more specific/granular topics on the use of digital infrastructure.
3. Determine the minimum resources, tools and best practices that emerging regulators would need to leverage common digital infrastructure technologies.

Other issues/areas for consideration

Topics that were raised during the breakout but could not be considered during the time available were ICH and ICMRA involvement in digital governance and policy development; leveraging transparency and trust initiatives from the RWD and patient engagement spaces to the digital infrastructure space; challenges for HTA agencies related to the administration of digital infrastructure and review of evidence; and developing digital infrastructure using an experimental multi-stakeholder 'sandbox' approach to allow early piloting and problem solving. The breakout group also highlighted the 'chicken and egg' issue of establishing common digital infrastructure; global harmonisation will enable use of digital infrastructure, but the development of digital infrastructure will also be a driving force for harmonisation.

Breakout discussion D

How are digital technologies being used to facilitate patient engagement strategies and the collection of patient-reported data – do new strategies need to be considered, particularly during accelerated development and review?	
Chair	**Dimitrios Athanasiou,** *Member of EMA Paediatric Committee and Eurordis; Board Member of World Duchenne Organisation, European Patient Forum and Greek Patients Association*
Rapporteur	**Saiza Elayda,** *Associate Director, Global Regulatory Policy, Merck & Co, USA*

Background

Digital technologies can facilitate patient input into drug development in a number of ways. Technologies like smartphone apps and wearable devices can be used to collect patient-reported data, either within a trial setting or in the real world as part of a natural history study or post-marketing surveillance. Online surveys can be a tool for gathering patient preferences in a quantitative manner, whilst virtual meeting platforms can facilitate qualitative patient input by directly connecting patient advocates with drug developers, regulators and HTA agencies as part of virtual multi-stakeholder meetings. In addition, social media is a patient engagement tool that offers opportunities in the areas of clinical trial recruitment and the collection of patient experience data, such as for pharmacovigilance purposes.

Although these digital technologies existed before COVID-19, it was not until the COVID-19 pandemic that they became widely used, as new ways of working had to be identified to cope with social distancing and travel restrictions. The expansion of virtual meeting platforms during the pandemic has increased patients' accessibility to meetings and events, thus facilitating discussion and exchange between patients and other stakeholders in an unprecedented manner [1].

Multi-stakeholder discussions during a CIRS workshop in 2020 highlighted a major opportunity in the use of virtual technology as a patient engagement tool [2]. However, it was also noted that virtual meetings cannot easily facilitate the networking and personal interactions that occur in face-to-face meetings, which can offer important opportunities for drug developers and regulators to learn from patients (and vice-versa) in a less formal manner. Furthermore, the COVID-19 pandemic has highlighted the challenge of adapting patient engagement strategies and the collection of patient-reported data to expedited procedures and timelines. For example, in the UK, it has been reported that there has been a decrease of studies containing public/patient involvement from 78% in 2019, to 20% in the first 40 trial submissions received during the COVID-19 pandemic [3].

Therefore, this breakout group examined the impact of digital technologies on patient engagement and whether new strategies need to be considered, particularly during accelerated development and review. The objectives were to discuss:

- **How are digital technologies being used to facilitate patient engagement** strategies and the collection of patient-reported data?
- **What are the current gaps/challenges and potential solutions** for utilising digital technologies for patient engagement?
- **What policies/tools are needed** to support patient engagement during accelerated development/review?

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Discussion results

Q1a. How are digital technologies being used to facilitate patient engagement strategies and the collection of patient-reported data?

Digital technology	**Examples of how it is being used for patient engagement**
Social media	Can be used as a tool to engage patients in research e.g. dissemination of surveys gathering patient experience data via external secure websites. Patient support groups can help to disseminate. Has been more prominently used during the COVID-19 pandemic e.g. collecting patient recovery experiences and information on the impact on the patient's family.
Mobile applications	Acute Respiratory Illness Surveillance (AcRIS) With Mobile Application in a Low-Interventional Decentralized Study collected information from patients using a mobile app, followed by a confirmatory test (swab for viral respiratory vector)
Wearables	Studies in Duchenne muscular dystrophy where patients wear devices linked to mobile apps, which provide feedback on ease of use. Important that developers are mindful of patient experiences and preferences e.g. the look and feel of the product.
Virtual meeting platforms	Facilitates patient input in agency processes
Electronic health records	Discreet access to electronic health records can facilitate patient recruitment e.g. COVID-19 testing centres informed patients on their potential to be enrolled in a clinical trial.

Q1b. Of the patient engagement strategies identified in Q1a, which two are most impactful and should be prioritised under accelerated development/review timelines?

The breakout group selected **social media and apps/wearables** (as both are interlinked) as the most impactful patient engagement strategies that should be prioritised under accelerated timelines. Social media was selected as it 'casts a wide net' and is easy to use, which can mean quicker responses from a more diverse group of patients. Apps/wearables were thought to be impactful for their potential to change patient behaviour as well as their ability to continuously monitor patients in real time.

Q2. What are the current gaps/challenges for utilising digital technologies for patient engagement and what could be potential solutions?

Q3. What policies/frameworks/tools or other research are needed to support patient engagement during accelerated development/review? Which organisations/groups should develop these?

Aspect of ecosystem	**What is needed?**	**Who should develop?**
Policies *Incentives, initiatives, funding, societal priorities*	• Organisation of information • Consistency and unification of information management • Centralisation of information • Prioritisation of health	Governments/regulators
Frameworks *Regulatory frameworks, tools*	• Safety • Input from various sources	Regulators collaborating with industry, patients, healthcare providers
Tools *Technological tools*	• New methodologies • New validation processes • Acceptance of methodologies used in other areas e.g. social sciences.	Collaborative effort with regulators, patient groups, industry
Research/Other	• How meaningful Patient Reported Outcomes (PROs) can be interpreted so clinicians can use information at point of care.	CIRS

Q4. Recommend future research projects for CIRS and other groups to undertake in this area - what should be considered to support the improve current activities?

1. Further discussion on policy and regulatory framework development
2. How to tie measurements by regulators or industry to what matters to patients
3. Development of new methodologies for validation of PROs
    a. PRO science – creating benchmarks for day-to-day use by clinicians
4. How to account for disparities among cultures and different socioeconomic populations

Appendix: Workshop attendees

Affiliations are stated as they were at the time of the meeting (24-25th June 2021).

Regulatory agencies		
Nurul 'Ain Bte Azman	*Senior Analyst*	*Ministry of Health, Singapore*
Nathalie Bere	*Patient Engagement*	*European Medicines Agency*
Dr Guei-Kore Valery Boidy Dakoury	*Pharmacist*	*Ivorian Pharmaceutical Regulatory Authority, Cote D'Ivoire*
Dr Claus Bolte	*Head of Sector Marketing Authorisation*	*Swissmedic*
Dr Florence Butlen-Ducuing	*Topic Lead in Psychiatry and Mental Health/Office for neurological and psychiatric disorders*	*European Medicines Agency*
Jung-Yui Chiou	*Associate Reviewer*	*Food and Drug Administration, Taiwan*
Dr Rian Extavour	*Technical Coordinator – Caribbean Regulatory System*	*Caribbean Public Health Agency, Trinidad and Tobago*
Dr Jenna Griffiths	*Manager*	*Health Canada*
Dr Laetitia Guillemette	*Risk Management and Regulatory Policy Advisor*	*Health Canada*
Li-Chen Huang	*Associate Reviewer*	*Food and Drug Administration, Taiwan*
Mei-Chen Huang	*Section Chief*	*Food and Drug Administration, Taiwan*
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Dr Hsien-Yi Lin	*Senior Reviewer*	*Food and Drug Administration, Taiwan*
Jane Mashingia	*Technical Advisor to the East African Community Medicines Regulatory Harmonization Programme*	*East African Community Secretariat, Tanzania*
Roslyn Neals	*Policy Analyst*	*Health Canada*
Cristobal Ortega Ramirez	*Health Surveillance Analyst*	*Institute of Public Health, Chile*
Mercy Owusu-Asante	*Head, Drug Industrial Support Department*	*Food and Drugs Authority, Ghana*
Dr Andrew Potter	*Mathematical Statistician*	*Food and Drug Administration, USA*
Andrew Raven	*Manager*	*Health Canada*
Dr Leonard Sacks	*Associate Director for Clinical Methodology, Office of Medical Policy, Center for Drug Evaluation and Research*	*Food and Drug Administration, USA*
Fan Shi	*Senior Biostatistician*	*Health Canada*
Tariro Sithole	*Projects Manager*	*Medicines Control Authority, Zimbabwe*
Adj Prof John Skerritt	*Deputy Secretary*	*Department of Health, Australia*
Dr Pat Stewart	*Director General, Therapeutic Products Directorate*	*Health Canada*
Yinghua Su	*Senior Biostatistician*	*Health Canada*
Dr Thorsten Vetter	*Scientific Officer*	*European Medicines Agency*
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Dr Li Ying (Grace) Huang	*Director, Division of HTA*	*Center for Drug Evaluation, Taiwan*
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Anne Lee	*Chief Pharmacist*	*Scottish Medicines Consortium, UK*
Lindsay Lockhart	*Public Involvement Advisor*	*Scottish Medicines Consortium, UK*
Dr Nicole Mittmann	*Chief Scientist and Vice-President, Evidence Standards*	*Canadian Agency for Drugs and Technologies in Health*
Tal Morginstin	*Director, HTA Division*	*Ministry of Health, Israel*
Dr Brian O'Rourke	*Former CEO* *Chair of HTA Steering Committee*	*Canadian Agency for Drugs and Technologies in Health* *CIRS*
Mark Salmon	*Programme Director – Information Resources*	*National Institute of Health and Care Excellence, UK*
Dr Sean Tunis	*Past President*	*HTA international*

Pharmaceutical companies and consultancies		
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Academic, non-profit and patient organisations		
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Natacha Bolanos	*Regional Manager Europe & Global Alliances Manager*	*Lymphoma Coalition, Spain*
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Prof Hans-Georg Eichler	*Professor of Clinical Pharmacology*	*Medical University of Vienna, Austria*
Dr Helga Gardarsdottir	*Associate Professor*	*Utrecht University, The Netherlands*
Prof John Lim	*Executive Director*	*Centre of Regulatory Excellence, Singapore*
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Valentina Strammiello	*Head of Programmes*	*European Patients Forum, Belgium*
Lorna Warwick	*CEO*	*Lymphoma Coalition, Canada*
Durhane Wong-Rieger	*President and CEO*	*Canadian Organization for Rare Disorders, Canada*

Centre for Innovation in Regulatory Science	
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Dr Magda Bujar	*Manager, Strategic Development*
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Juan Lara	*Research Analyst*
Dr Lawrence Liberti	*Senior Advisor*
Dr Neil McAuslane	*Director*
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