

The New Frontiers Meeting in Digital Health

10-11 March 2019, Nice, France

Meeting Report

Abstract

The New Frontiers Meeting in Digital Health (10-11 March 2019, Nice, France) brought together pharma, academia, health care, regulatory agencies, SMEs and patient groups to evaluate the emerging role of digital medicine in developing new approaches and therapies for brain disorders. Over 100 participants attended with a unique and wide range of expertise, providing valuable insights into many aspects for the potential of digital technologies to improve the diagnosis, treatment and monitoring of health. It highlighted several technical, ethical and regulatory issues that need to be addressed as the field develops in the coming years. The potential and issues of digital approaches in clinical trials for new treatments for brain disorders will be the focus of the next New Frontiers on Digital Health Meeting. Topics will include digital therapeutics as treatments, new approaches to the diagnosis and monitoring patient outcomes and a preliminary program and details on how to attend can be found [here](#).

Report

The New Frontiers Meeting in Digital Health (10-11 March 2019, Nice, France) was convened by the ECNP to discuss and evaluate the emerging role of digital medicine in developing new approaches and therapies for brain disorders. Over 100 participants attended, from pharma, academia, health care, regulatory agencies, SMEs and patient groups representing a unique and wide range of scientific, technical, regulatory and patient expertise in this fast-growing area.

The program and its participants aimed to: (i) identify the basic principles, opportunities and strategies for developing digital methods and therapeutics to advance the treatment of brain disorders; (ii) identify, the technical, ergonomic, regulatory and scientific barriers to the development of digital medicine; (iii) share experiences, challenges and technical knowledge on how to address the potential and limitations of digital medicine; and (iv) consider the ethics of the unprecedented access to the lives of patients that digital technologies can provide.

The meeting was chaired by ECNP president Celso Arango and focused on (i) the latest advances in wearable technologies and digital therapeutics, (ii) EU projects focused on digital technology and medicine, (iii) regulatory and patient/family associations perspective on digital medicine, and (iv) the innovative use of digital medicine. This brief meeting report summarises and synthesises the proceedings and outcomes of the meeting and sets the stage for the next meeting in this series which will be held in Nice, France (8-10 March 2020). For more details on the programme and how to apply to register your interest please see [here](#). Members of the programme [committee](#) welcome suggestions for themes and speakers for future meetings.

Background

The WHO recently published [recommendations](#) on digital interventions for health system strengthening urging readers to recognise that digital health interventions are not a substitute for functioning health systems, and that there are significant limitations to what digital health is able to address. Meanwhile financial analysts McKinsey were [urging readers](#) to embrace the \$100-billion

opportunity that digital medicine offers. The mental health community is already receiving the attention of those who are concerned about the latter and the former and who see a therapeutic (and financial) opportunity.

That should not be a surprise; for example, a recent UK report¹ stated that mental health problems account for a quarter of all ill health in the UK, that one in four adults will experience mental health problems each year, and that mental illness is the UK's single largest cause of disability. Add to this that almost a third of all people with any long-term physical health conditions also have a mental health problem, typically depression or anxiety² and the scale of the issue becomes apparent.

It is widely assumed that readily available digital technology can go some way to alleviating the patient and societal burden and there are a rapidly growing number of mental health applications (apps) available for digital devices such as tablets and smartphones. However, they bring with them uncertainty. There is very little regulation and minimal information on apps' validity and effectiveness, it is often not known whether these apps are evidence-based, or even if they contain potentially harmful content. Consequently, research carried out in 2016, cautioned clinicians against recommending apps for supporting people at risk of suicide.³

To consider these emerging technology-driven opportunities and pitfalls and their impact on health outcomes the ECNP programme opened with two keynote speakers. The first keynote by Esther Rodriguez-Villegas, posed the question: '*Wearable technologies: do they have a role to play either as research tools or as medical devices*' and the second by Nathan Cope: '*Digital medicine: changing perceptions for the treatment of mental illness*' described a medical device that enabled close monitoring of treatment (drug) compliance.

Esther is professor of Low-Power Electronics at Imperial College, and recently has focused her research on life-science applications, founding the Wearable-Technologies-Lab and is founder of two active life-sciences companies, Acurable and TainiTec. She described how patients need technologies that are easy to use and do not require a health care professional to interpret the data. By doing so they can be empowered to manage their own health (self-care) using information that is readily available (e.g. heartrate, blood pressure, etc.) and can assist a physician when an intervention is required. She underlined that the challenge with this approach is that the such sensors need to be not only unobtrusive and low maintenance, but to be truly useful they need to have sensitivity, specificity and reliability. Although much of this data can be obtained from devices such as smartphones and fitness wearables, these devices are not CE marked (certified) medical devices and the data recorded by them may lack the accuracy and specificity to be useful in health care. Developing wearables that are safe, reliable and meet regulatory requirements for sensitivity and specificity remains a challenge.

In the second keynote lecture Nathan Cope (European Digital Health Director, Otsuka) described Otsuka's digital health efforts in mental health. Otsuka is probably best known for their development of anti-psychotic drug, aripiprazole, which is marketed in the US through a partnership with Bristol-Myers Squibb. Nathan described how 'Abilify MyCite', a digital sensor manufactured by Proteus Inc. and embedded in a pill which records medication adherence and vital parameters, has changed the way individuals affected by schizophrenia (SZ) can monitor treatment compliance, a problematic issue for this population. However, human factor studies with this device have posed a challenge, the huge amount of data that resulted from the clinical trials that were conducted for regulatory approval requiring significant management and careful analysis. Nonetheless, it is clear that this device plays a large role in providing patients and potentially clinicians/relatives with more awareness and control over their health and medication.

The following day the programme began with an exciting and informative session, chaired by Hugh Marston (Lilly, Europe), on a selection of *Digital health projects funded by the European Union (EU)*. Matthew Hotopf (Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK) began the session with a description and update on the activities of RADAR-CNS (Remote Assessment of Disease and Relapse). RADAR-CNS (www.radar-cns.org) is developing new methods of monitoring major depressive disorder, epilepsy, and multiple sclerosis using wearable devices and smartphone technology and is funded by the Innovative Medicines Initiative (IMI), a partnership established between the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the EU. The systems are built on open-source platforms and aim to actively and passively continuously collect data. Initial studies in patients with major depressive disorder (MDD) use remote measurement technologies (RMT), including smartphones, apps, and wearable devices to track MDD symptoms with the aim of effectively managing symptoms or to predict their onset. Initial results from patient acceptance studies indicate good participant adherence to the study requirements and high levels of participant satisfaction with the system. However, individual variability in passive data collected may reflect the limitations in using commercially available smartphones and wearables where the components are not of medical grade, an issue raised earlier by Prof. Rodriguez-Villegas and an issue that flowed through the meeting.

Martien Kas (professor of Behavioural Neuroscience, University of Groningen, the Netherlands) continued the session with an outline of the PRISM (Psychiatric Ratings using Intermediate Stratified Markers, <http://prism-project.eu/>) project that is providing quantitative biological measures to facilitate the discovery and development of new treatments for social and cognitive deficits in Alzheimer's disease (AD), schizophrenia (SZ) and major depression (MDD). PRISM is also funded by IMI2. The project focuses on social withdrawal as a common early symptom of many brain disorders. However, the underlying, biological causes of these symptoms are still poorly understood and may differ from one disease to another. Rather than classifying patients according to diagnostic criteria, the PRISM project aims to determine which biological parameters correlate with specific clinical symptoms, like social withdrawal, that are common across disorders⁴. The aim is to develop treatments based on patients' symptoms that are linked to validated biological biomarkers rather than a diagnostic classification. As an example of this approach, Prof. Kas described how to assess longitudinal and objective measures of social withdrawal in a trans-diagnostic manner across species. Comparing traditional questionnaire measures of social withdrawal with passive data obtained for BEHAPP (a smart phone app that records call and messaging history, location data, social media usage, etc.) from patients with AD, SZ and healthy age matched controls highlighted aspects of social withdrawal that could only be obtained from digital profiling. The next step is to link these aspects of social withdrawal to biological systems, which is the subject of a PRISM clinical trial that will complete later this year. Full and detailed description of the project and its methods can be found in a [special edition](#) of *Neuroscience and Biological Reviews*.

How to better treat and manage depression using a digitally support pathway was described by Guy Goodwin (Department of Psychiatry, University of Oxford, UK and P1vital UK). The PReDicT project (Predicting Response to Depression Treatment, <https://predictproject.p1vitalproducts.com/>) completed a European-wide study to validate the clinical performance of the P1vital® PReDicT Test, a novel medical device to improve the treatment and management of depression in clinical practice. The study was funded by the EU Horizon 2020 SME programme. The PReDicT test uses a machine learning algorithm to provide a rapid and objective measure of a patient's response to an antidepressant which accelerates their recovery from the illness. In an ~950 patient study that has just completed comparing treatment as usual to treatment managed by PReDicT, early analysis suggests the medication switches occur much earlier in treatments for patients in the PReDicT arm. Although this did not significantly reduce symptoms of depression compared to controls, it did significantly reduce comorbid symptoms of anxiety. As with RADAR-CNS, patients were highly

compliant with the requirements of the digital technology and placed high value on the support it provided. Six-month outcome and health economic data will be available later in 2019.

The MONARCA Project (MONitoring, treAtment and pRediCtion of bipolar Disorder Episodes, <https://cordis.europa.eu/project/rcn/93747/factsheet/en>) was presented by Maria Faurholt-Jepsen (Psychiatric Center, Copenhagen, Rigshospitalet, Denmark). Mood instability in bipolar disorder is associated with a risk of relapse and the MONARCA study investigated differences in mood instability between patients with bipolar disorder type I and type II symptoms. Patients with bipolar disorder type I and type II used a daily smartphone-based self-monitoring system for approximately 9 months. It showed that patients with type II disorder experienced more mood instability during depression compared with patients with type I. They also had lower intensity of manic symptoms and did not experience lower mood or higher intensity of depressive symptoms compared with patients with type I disorder. This early digitally enabled study showed that type II patients had higher mood instability for depression and indicated that the effect of treatment on mood instability requires further research.

In the second main theme of the meeting chaired by Hilka Karkkainen President of GAMIAN-Europe, *Regulatory and patient/family association perspective on digital medicine*, Luca Pani (professor of Clinical Psychiatry at the Department of Psychiatry and Behavioral Sciences, University of Miami, and professor Pharmacology and Clinical Pharmacology, University of Modena and Reggio Emilia, Italy) opened this session with a review of regulatory issues in digital medicine. As a former head of the Italian regulatory agency and with a particular interest in health technology assessment, Prof. Pani challenged the meeting participants to consider whether we are ready for the realities of reconciling big data and patient privacy in Europe. The new EU General Data Protection Regulation (GDPR, 2018) is driven by the principle of data minimisation and includes the right to privacy as a default and if it is not accounted for in the early stages of research may hinder future data mining. It is clear that artificial intelligence (AI) enabled machines will not fully replace human care and the systems that work best will be those that successfully blend functions that machines do better than humans (*e.g.* continuous monitoring of vital signs) with those that are best suited to healthcare professionals (*e.g.* end of life care).

David Reynolds (CSO, Alzheimer's Research UK, ARUK) continued this session with a review of two recent surveys on public attitudes on the early detection of dementia in the UK (sponsored by ARUK) and across Europe (sponsored by MSD). A significant change in recent years is the public's understanding that dementia is caused by a disease and is not an inevitable consequence of growing old. Despite the lack of treatment many people would like to be told of their risk of developing dementia or indeed if they had the disease. And while many individuals are willing to have a diagnosis made by a minimally invasive method (eye or blood test, brain scan, cognitive testing, etc.) they are less willing to accept a diagnosis made by computer or smartphone app. Moreover, less than half the patients questioned would be willing to undergo a lumbar puncture, the currently most reliable method for diagnosis specific dementias. Finally, it is clear that the opportunity for early detection of dementia's by digital means is huge, and that a composite fingerprint of endpoints will be required to ensure sensitivity and specificity of this approach.

Finally, in this session, Pim Haselager (Donders Institute for Brain, Cognition and Behaviour, Department of Artificial Intelligence, Radboud University, Nijmegen, the Netherlands) identified some of the likely pinch points when ethics meets digital health by examining how AI technology can affect users (patients, physicians, family). He emphasised that it is important to consider that data collected for one purpose can easily be used for another. He used the example of 'functional creep' in the criminal justice system as an illustration of how personal individual data can be merged from multiple databases (*e.g.* tax, health, property) to create a digital profile of an individual that may

predict (using AI) their propensity for criminal behaviour. In health systems as the use of smart technology grows among the general population, some predict an accompanying blurring of medical and everyday devices, that can create privacy concerns, run the risk of errors, and may mislead patients. Moreover, they may provide an opportunity for multi-national providers of smartphones and apps to comment on an individual's health or provide services directly to patients. This could result in a fundamental shift in what is meant by the 'doctor-patient relationship' as apps may insert more distance (both physical and emotional) between doctor and patient. Dr. Haselager concluded that AI is more than an additional technique for exploring and using data to predict outcomes, it is in practice a restructuring force that necessitates a broader relational perspective and wider debate.

In the final session '*Innovative use of digital technologies*' chaired by Gerry Dawson (P1vital Ltd), Tom Craig (Emeritus Professor, IoPPN, King's College London, UK) described how virtual reality (VR) can be used in many ways in mental health including probing to better understand psychopathology, create social interactions (e.g. face to face conversations) and create 'safe spaces' to manage exposure to threat, paranoia and practice coping. He described how he has used VR to conduct AVATAR therapy for auditory verbal hallucinations in people with psychosis. In this new approach patients hear a digital representation (avatar) of their persecutor that is voiced by their therapist. The therapist coaches them to respond in a way that reduces the hostility and power of their persecutor. In a large-scale study 150 patients were randomly assigned to receive either AVATAR therapy (n=75) or supportive counselling (n=75). The reduction in Psychotic Symptoms Rating Scales Auditory Hallucinations (PSYRATS-AH) at 12 weeks was significantly greater for AVATAR therapy than for supportive counselling. Overall AVATAR therapy is cost effective, had better outcomes and did not result in recordable adverse events. Interestingly, approximately 21% of patients declined the offer of AVATAR therapy suggesting that there are some barriers to the acceptability of this approach among patients.

Deborah Kilpatrick (Chief Executive Officer, Evidation Health, CA, USA) described the Evidation platform on which knowledge about health and disease can be derived from high-frequency digital data with patient consent. One aspect of Evidation's work is to consent and enrol participants from across the USA to provide patient-generated health data (PGHD) for research protocols and digital biomarker development via connected devices and smartphone/smartwatch apps. In doing so participants provide real-world data without the need to attend a clinical site for assessment. Using this approach, the company recruited 10,000 patients for a 12-month study of chronic pain based on data gathered from a combination of wearables, environmental data, online surveys, and laboratory tests using at-home sampling approaches. Such virtual methods can significantly reduce recruitment time and costs for clinical research while enabling the study sample to better reflect real world patient populations. The breadth of applicability of these approaches depends on many factors, including the feasibility of correlating PGHD with relevant measures confirming disease status, which can be challenging to quantify in many mental health conditions. In addition, it is essential to ensure study and data quality and security is maintained through credentialing procedures such as two-step verification/dual factor authentication and other relevant operating procedures.

Finally, Andy Coravos (CEO/co-founder of Elektra Labs) described how she is building a digital medicine platform with an initial focus on digital biomarkers for decentralised clinical trials^{5,6} that are safe, effective and ethical. She emphasised that for digital medicine where we intend to measure (digital biomarkers), diagnose (digital diagnostics) and treat (digital therapeutics) we need to develop and build clinically validated software and algorithms. In developing digital biomarkers, we will need to first define what kind of biomarker it is (monitoring, diagnostic, pharmacodynamic, predictive, safety or susceptibility/risk) and how that data will be collected. Data collected to create a 'digital biomarker' often is generated from a wearable or biosensor of app, remotely at home, work or social environment (e.g. outside of the clinic). Collection of digital biomarkers by relatively inexpensive

means. The number of FDA-cleared software medical products, such as Apple's series 4 watch with FDA-granted ECG, is rapidly increasing. Other applications of digital technologies are leading to the decentralising of clinical trials resulting in a reduction of clinical trial infrastructure (physical sites and study personnel who historically have recorded and entered data). Participants no longer need to be in the immediate vicinity of a physical trial site to participate in a clinical trial, as data can be recorded digitally via apps or by more mobile personnel (*e.g.* mobile phlebotomist). As these digitally driven changes are rolled out the regulatory agencies need to adapt and responded to this rapidly changing environment. This can be difficult because software itself, for example, can be a medical device (if used for diagnostic purposes – software *as* a medical device) or it can be incorporated in a medical device (*i.e.* software *in* a medical device, such as that found in a connected blood infusion pump). Agencies such as International Medical Device Regulators Forum (IMDRF) and the National Institute for Health and Care Excellence (NICE) are now racing to issue frameworks and guidance of the safe and effective use of digital health technologies (see further [here](#)). As connected tools track more data remotely, new frameworks around governance and rights for these digital specimens becomes critical. Currently, there is largely a regulatory gap around digital specimen protections.⁷

Concluding remarks

Prof. Arango concluded the meeting by thanking the participants. The presentations and discussion provided valuable insights into many aspects for the potential of digital technologies to significantly improve the diagnosis, treatment and monitoring of health. It also highlighted several technical, ethical and regulatory issues that need to be addressed as the field develops in the coming years. The potential and issues of digital approaches in clinical trials for new treatments for brain disorders will be the focus of the New Frontiers on Digital Health Meeting in Nice 2020. Topics will include digital therapeutics as treatments, new approaches to the diagnosis and monitoring patient outcomes. A preliminary program for the meeting can be found [here](#), and if you are interested in attending the meeting please submit your application on the website.

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