CDDF
Cancer Drug Development Forum

MEETING REPORT

CDDF Multi-Stakeholder Workshop

Digital Tools and Artificial Intelligence in Oncology Drug Development

27-28 September 2021
Online Workshop
Prepared by the CDDF

PROGRAMME COMMITTEE

Chair: Ruth Plummer (CDDF),
Nafsika Kronidou Horst (Roche)
Ralf Herold (EMA)
Denis Costello (CML Advocates Network)
Dónal Landers (digital Experimental Cancer Medicine Team, CRUK Manchester Institute)

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Introduction

The workshop was designed to evaluate the current state of play in terms of the opportunities for use and regulatory perspectives as increasing numbers of digital tools are being incorporated into clinical trials. The integration of such tools into trials is bringing challenges in terms of validation of endpoints, interpretation of data and also data security. The program committee of Ruth Plummer (CDDF board), Nafsika Kronidou Horst (industry partner, Roche), Ralf Herold (EMA), Denis Costello (patient advocate) and Dónal Landers (academic partner) developed a 2 day workshop to address these elements.

The main learning objectives from the workshop were:

- To understand the current landscape on the use of digital tools in cancer drug development
- To explore regulatory aspects, challenges and plans for formal registration of digital tools from trial data
- To learn about the various digital options to support the design trials and improve data collection and outcomes

The workshop took place virtually over 2 days on 27th and 28th September 2021, with 187 registrants and 58 active participants during the live-streamed meeting. The majority of participants were from US, UK and Belgium, with additional attendees from other European countries.

Program

DAY 1 - 27 SEPTEMBER 2021

SESSION 1: APPLYING AI IN CLINICAL DRUG DEVELOPMENT – KEY CHALLENGES
Session chair: Ruth Plummer (CDDF, UK)

Keynote lecture
Dónal Landers (digital Experimental Cancer Medicine Team, CRUK Manchester Institute, UK)

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Endpoints using digital tools
Chris Plummer (Newcastle Hospitals NHS Foundation Trust, UK)

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Ib Alstrup (Danish Medicines Agency, DK)

Panel Discussion

SESSION 3: CLINICAL DECISION SUPPORT TOOLS AND CLINICAL PRACTICE
Session Chairs: Nafsika Kronidou (Roche, CH); Torsten Haferlach (Munich Leukemia Laboratory, DE)

Regulatory considerations on EU trustworthy AI
Gabriele Mazzini (European Commission, IT)

Digital Diagnosis
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How AI can support best diagnostic approaches in haematology
Torsten Haferlach (Munich Leukemia Laboratory, DE)

Panel Discussion

DAY 2 - 28 SEMPTEMBER 2021

SESSION 4: DIGITAL TOOLS SUPPORTING INNOVATIVE PATIENT CARE
Session Chairs: Denis Costello (CML Advocates Network, ES); Jan Geissler (Patvocates, DE)

Patient perspective
Hans Scheurer (Myeloma Patient Europe, NL)

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Session chairs: Nathalie Bere (EMA, NL) ; Dónal Landers (digital Experimental Cancer Medicine Team, CRUK Manchester Institute, UK)

Patient engagement in designing the clinical studies
Leanna Goodwin (Digital Experimental Cancer Medicine Team, CRUK Manchester Institute, UK)

Design and delivery of the In-home study
Leanne Phillips (Manchester Foundation Trust; Digital Experimental Cancer Medicine Team, UK)

Data security and regulation
Petra Wilson (Health Connect Partners, BE)

Panel Discussion

Session 1: Applying Ai In Clinical Drug Development – Key Challenges

Keynote lecture

Dónal Landers (digital Experimental Cancer Medicine Team, CRUK Manchester Institute, UK)

This plenary lecture was given by Dr Dónal Landers from the digital Experimental Cancer Medicine Team (ECMT), CRUK Manchester Institute, UK. In the presentation he addressed some of the main challenges confronting the application of AI in drug development and healthcare in general. In particular, he discussed the current 'AI' hyperbole, giving examples of what AI is and is not. He illustrated some of the key questions which need to be addressed before deploying AI in a clinical setting. Examples were given of deep learning typologies, training problems associated with some of these algorithms and how bias can inadvertently occur because of the choice and design of the training dataset. The presentation also covered the important principles of 'ethical AI' and provided a model of how the digital ECMT in Manchester is addressing the application of AI in a clinical setting through the concept of a 'Technology' clinical trial, which is similar to the way a drug trial is conducted – and has developed a tool kit for the regulatory set up of such trials.

Session 2: Digital tools in clinical trials

In this first panel session of the workshop the first three speakers discussed examples of digital tools being used within trials and the final speaker spoke to the regulatory aspects of these interventions.

Digital tools in trials for monitoring

Larsson Omberg (Sage Bionetworks, US)

Larsson Omberg (Sage Bionetworks, USA) discussed the fact that digital measurements offer a unique opportunity to measure the lived experience with disease. He illustrated that frequent data collection through both passive and active data streams allows us to collect real-world data that represents the interaction between disease symptoms and a person's life. He argued that this provides both a unique opportunity but also complicates the development and validation of novel measures as well as study design and analysis of digital health data. This was illustrated using examples of environmental perturbations such as weather, Covid-19, and being observed that may affect performance on several health measures. He discussed analytical approaches being developed for handling this data and how open and collaborative approaches can be used to accelerate the development of validated and benchmarked measures.

Endpoints using digital tools

Donna Graham (The Manchester Digital ECMT, UK)

The session co-chair, Donna Graham (The Manchester Digital ECMT, UK) gave an oversight of clinical trial endpoints and how these can be adapted for digital tools. This was framed by introducing the concept of the technology clinical trial incorporating a formal evaluation of the technology and the clinical benefit. The opportunities to create new endpoints or adapt endpoints was highlighted with a focus on clinically meaningful benefit as the critical element. The framework developed by the National Institute for Clinical Excellence in the UK was discussed with signposting to the Digital Medicine Society's library of digital endpoints as a

resource for endpoints currently under evaluation in clinical, academic and industry-sponsored research.

Digital tools for recruitment

Chris Plummer (Newcastle Hospitals NHS Foundation Trust, UK)

The third speaker in the session, Chris Plummer (Chief Clinical Information Officer, Newcastle Hospitals NHS Foundation Trust, UK) illustrated the power of digital tools to aid recruitment to clinical trials. Healthcare systems across the world are currently transitioning to the digital acquisition, consumption, analysis and communication of data, involving patients in the direct two-way exchange of information in new ways. He illustrated that this provides opportunities for delivering current healthcare and research into future treatments, using these innovative digital tools. While many healthcare systems have already achieved high levels of digital maturity, less enabled systems also have rich data which could transform clinical and research practice, within the appropriate legal and governance processes. However, to achieve this potential will require the trust of citizens and healthcare professionals, and a systematic approach to digital-enabled research using artificial intelligence tools. This would enable us to assess the prevalence and incidence of patients fulfilling trial inclusion and exclusion criteria, real-time screening across electronic patient record systems, and the acquisition and reconfirmation of patient preferences about research, with the use of trusted websites and social media to identify participants. His proposal was that we are at the start of a revolution in clinical trial design, recruitment, and delivery and that working in partnership between patients, researchers, healthcare systems and industry, we will be able to deliver better outcomes for our patients now and in the future, in greater safety, more quickly and at lower cost.

Regulatory aspects

Ib Alstrup (Danish Medicines Agency, DK)

To conclude the session Ib Alstrup, Medicines Inspector, GxP IT, at the Danish Medicines Agency (DKMA) gave an overview of focus areas when performing regulatory inspections of traditional digital tools used in clinical trials. He referred participants to the new EMA Guidance on Computerised Systems in Clinical Trials. The presentation also included an overview of a proposal by the DKMA for questions when evaluating digital tools including AI/ML algorithms.

Session 3: Clinical decision support tools and clinical practice

This session discussed a range of aspects on the use digital tools to aid clinical decision making.

Regulatory considerations on EU trustworthy AI

Gabriele Mazzini (European Commission, IT)

Initially Gabriele Mazzini (European Commission, IT) discussed the Commission's proposal for an AI Act which aims to provide AI developers and users with clear requirements and obligations regarding specific uses of AI. This Act covers all industry sectors including healthcare. The proposed AI regulation will endeavor to ensure that Europeans can trust what AI has to offer. This will be obtained through a proportionate risk-based approach. While most AI systems pose limited to no risk and can be used to solve many societal challenges, certain AI systems create high-risks that need to be addressed to avoid undesirable outcomes.

As regards high-risk systems, the proposed rules would identify a specific list of use cases, set clear requirements applicable to them, define specific obligations for users and providers,

establish a conformity assessment before the AI system is put into service or placed on the market, set up an enforcement system after such an AI system is placed in the market and propose a governance structure at European and national levels. The EU proposal foresees also specific prohibitions for AI systems that pose an unacceptable risk (from social scoring by governments to manipulative or exploitative AI systems). For example, the live use of remote biometric identification systems in publicly accessible spaces for law enforcement purposes is also prohibited in principle, but three narrow exceptions are possible (such as where strictly necessary to search for a missing child, to prevent a specific and imminent terrorist threat or to detect, locate, identify or prosecute a perpetrator or suspect of a serious criminal offence).

In those cases where AI systems pose only limited risks related to transparency, the proposal introduces specific disclosure obligations: for instance, when using AI systems such as chatbots, users should be aware that they are interacting with a machine and not a human. However, the speaker emphasized that the vast majority of AI systems currently used in the EU present minimal or no risk and are therefore not affected by the provisions of the proposed AI Act.

Digital diagnosis

Joachim H. Schmid (Roche Tissue Diagnostic, US)

Dr. Joachim H. Schmid (Roche Tissue Diagnostics) followed with a presentation focused on opportunities to use of digital tools in diagnosis using as an example the Roche Diagnostic "Navify" digital pathology platform He gave an overview of the comprehensive digital pathology platform they have been developing. This development team aimed to establish an ecosystem which includes multiple components to deliver a superior interface, developing scanners, and pathologist interface and also image analysis applications and algorithms – which he sees as key components to enable AI in this setting. He also highlighted the importance of establishing common standards in digital pathology and AI and briefly summarised ongoing global efforts. Finally, he introduced the concept of Good Machine Learning Practice (GMLP) analogous to GCP or GMP as a way of ensuring standards of algorithm development and validation are met.

How AI can support best diagnostic approaches in haematology

Torsten Haferlach (Munich Leukemia Laboratory, DE)

The final speaker in the session and co-chair, Dr Torsten Haferlach (Munich Leukemia Laboratory, Germany) discussed the use of digital diagnostic approaches in hematology, i.e. leukemias and lymphomas. He outlined the diverse and heterogeneous diseases which have been increasingly stratified over the last 20 years. The main reason for this is the dramatic increase in knowledge of genetics and especially molecular genetics behind the respective disease. He illustrated that it is now possible to implement whole exome sequencing (WES) whole genome sequencing (WGS) and whole transcriptome sequencing (WTS), in research and then stepwise into our clinical routine approaches.

Current WHO standards are defined by cytomorphology, immunophenotyping, standard chromosome banding analysis via metaphases, and normally by panel sequencing for molecular genetics. These different methods are combined per patient with respect to the suspected diagnosis. Dr Haferlach explained that in recent years AI has been introduced into our daily life, especially in our private life with many algorithms now used. These algorithms can also be used in research for the diagnoses and prognostication in leukemia. The Munich Leukemia Laboratory is already running several big trials, together with AWS and MetaSystems, to identify better diagnostic approaches using the differential blood count, the bone marrow differential, the immunophenotyping using specific labeled antibodies,

chromosome banding analysis as well as the interpretation of panel sequencing and also WGS and WTS. These strategies are now very close to being introduced in routine diagnostics, and in the last 2 years implementation of accredited cytogenetics by metaphase banding, supported by AI, in the clinic.

Session 4: Digital tools supporting innovative patient care

In this 4th session of the workshop the focus was on individual perspectives on how digital tools can support and transform patient care. This was discussed frow the patients' perspective, a clinician's and then the regulatory side

Patient perspective

Hans Scheurer (Myeloma Patients Europe, NL)

The patient perspective was presented by Hans Scheurer (WECAN, MPE, Netherlands) posing first the question "What do digital tools add for patients?" '

He explained that in the daily practice patients, as well as HCP's, experience difficulty of getting used to a new solution, working with it, actively using it and experiencing the benefits of the time and energy invested in integrating into daily practice. Digital solutions that work well and smooth, and are fully integrated in the system in use, have the highest acceptance and impact.. Patients then experience a closer involvement in what happens around them: being better informed, better able to ask your questions to the HCP, and all interaction is more real-time and potentially faster.

Many clinicians have been hesitant to share medical outcomes and reports with patients. Research on shared-decision-making shows nevertheless that a better-informed patient makes a doctor's visit more efficient and meaningful. It is very worthwhile to invest in a faster available and better understandable presentation of the medical results for patients. Digital health solution can contribute to this.

His second discussion point was based around "Why does technology need to be trusted?" He explained that for trust to develop, it needs transparency on what the digital tool or application does and also what it does not include. Regulation also needs to catch up fast with the digital world. Algorithms are formulas: so it matters what you include, and it should be clear what the tool measures, calculates, and also what is omitted. Patient should also be informed if data are collected for other reasons such as selling to third parties as a business model. The audience was informed was that patients would not want this with the medical data provided when using digital tools.

In the third section of his presentation Mr. Scheurer discussed "Patient centricity, how to get there?" He proposed that Developers need to get in touch with the patient group from the start of any project. They should also be aware that digital technology can be intimidating, and that picking just a 'patient representative' who is available to tick the 'patients involved' box might not give you that meaningful patient input needed for a better solution. It is always better to contact a patient group to find the right one you need. He also suggested that patient groups should be educating their representatives and collecting the preferences regularly and in a professional way. This would enable meaningful input in development processes of new digital solutions. Investing in understanding the digital developments in health care is an important aspect to then being able to be part of the debate.

Clinician perspective

Sanna Iivanainen (Oulu University Hospital, FI)

The clinician perspective was presented by Dr Sanna Iivanainen (Oulu University Hospital, Finland), outlining the potential advantages in the use of digital tools using patient reported

outcomes (ePROs) and also systematic symptom/side effect collection. She explained that cancer patients suffer from a variety of symptoms derived from the malignancy itself and some also arising as side effects of the given treatment. Many symptoms are left undocumented due to factors such as limited follow-up between prescheduled health care visits, non-systematic evaluation of symptoms, and inadequate communication. Emerging data have shown that electronic health record-based predictive algorithms may improve clinicians´ prognostication and decision-making. Compared to traditional follow-up of cancer patients, ePROs enable capturing of symptoms in timely and comprehensive manner and this integrates the patients` perspective into the cancer care continuum. The monitoring of changes over time may better predict treatment side effects and potential benefit than just a single presentation of a symptom. Large scale symptom data bases coupled with treatment benefit and side effects could be used to build prediction models using artificial intelligence methods. These models could predict risk for an individual patient for symptom development, treatment related side effects, and treatment benefit.

Regulatory aspects

Bleddyn Rees (European Connected Health Alliance, IE)

This topic was spoken to by Bleddyn Rees (European Connected Health Alliance, IE). He explained this alliance is a multistakeholder ecosystem which attempts to break down silos to advance developments in healthcare. To set the scene he illustrated that digital tools apply in all sectors of the healthcare system, from health and social care, well-being services through to housing and education. He raised a note of caution that the speed of innovation in the development of technology rapidly outpaces any change in law. He also gave examples of what may be considered a digital tool, from apps providing healthcare information, wearable devices to software which predicts health events. He also asked us to consider that the “med tech” sector is global, however health care provision is regional or national. This is having the consequence that different regions are “re-inventing the wheel” and also failing to learn lessons across borders from previous processes. There have been ongoing discussions about this complex legal issue within the EU over the last decade with the European Commission developing a regulatory overview in 2008 and pending legislation with the AI Act, Data Act and Data Governance Act. In conclusion he summarised that regulation should not be a barrier to innovation but ensure a balance between the benefit and safety for patients.. In the digital world problems can arise as much from too few regulations as from too much.

Session 5: Integration of patients in digital tool trial design and development

The final session of the workshop again focused on the needs and input of patients and how these important factors can be integrated into the design of studies using digital tools.

Patient engagement in designing clinical studies

Leanna Goodwin, (Digital Experimental Cancer Medicine Team, CRUK Manchester Institute, UK)

In the first talk Leanna Goodwin, (Manchester Digital ECMT, UK), a research practitioner who recruits patients to early phase clinical trials discussed their local experience with involving patients in trial design. Her talk outlined the work that the digital Experimental Cancer Medicine Team undertakes to ensure that patient involvement and engagement is embedded throughout their Clinical Trials. She stated that patient involvement and engagement is widely recognised as being impactful in the design, development and conduct of clinical research. Understanding the experience of patients and using learnings from this to inform the design of clinical research results in greater potential benefit for the wider patient population. Patient

engagement also encourages the process of taking part in research to be acceptable to the participants, and therefore encourages recruitment and retainment. Clinical research which involves digital tools often consists of novel processes which demand that participants in these trials take on a more active role than would be asked of them in other types of clinical research. This arguably makes patient involvement and engagement in the entire process of this research particularly important. In the digital Experimental Cancer Medicine Team, their main research focus is Technology Clinical Trials, which look to test a technology or digital solution under the same clinical trial conditions as those used to test new drug treatments. These trials aim to give patients the opportunity to become co-researchers, and to actively participate in their treatment by being directly involved in the development of new technologically enabled care pathways.

Design and delivery of the In-home study

Leanne Phillips (Manchester Foundation Trust; Digital Experimental Cancer Medicine Team, CRUK Manchester Institute, UK)

Leanne Phillips from the same institution (Manchester Digital ECMT, UK) then spoke about how they had worked with patients to design and deliver the "In-home" study. She outlined the background and unmet clinical need that lead to the idea of developing a body of work with the overall aim of pushing cancer clinical trials to becoming more inclusive and representative of the real-world population. Patients with many comorbidities are excluded from clinical trials and this research work focuses on patients with kidney dysfunction and cancer. The IN-HOME study is a first step in exploring this field. The trial aims to evaluate whether the monitoring and diagnosis of AKI in cancer patients can be improved using home digital tools. Subsequently the team would hope to be able to use this in patients who have established kidney disfunction to allow them to be enrolled more safely in cancer clinical trials.

Data security and regulation

Petra Wilson (Health Connect Partners, BE)

In the final presentation of the session Petra Wilson (Health Connect Partners, BE) discussed the important issues of data security and regulation. GDPR is a core tool for the lawful conduct of clinical trials and can play a crucial role in supporting patient engagement if used appropriately. The presentation set out the 7 key principle of the GDPR and their application to clinical trials: processing data for an explicit purpose, ensuring that data is adequate for the purpose, but relevant and limited only for that purpose. It must be processed securely and stored only as long as necessary. The presentation outlined the challenges of the limitation of data use principle and the role of consent in clinical trials. It also introduced the emerging concept of dynamic consent, focusing on the EnCore Project, which developed a new approach to consent which allows trial participants to dynamically interact with the consent process so that consent can be modified as participants progress through a trial.

Conclusion

Overall, the workshop covered a wide range of topics, using practical examples of digital tools and AI used in clinical trials to stimulate active discussion in the panel sessions about the opportunities and challenges of this approach within clinical trials. Overall, the evaluation of the content provided by the speakers was excellent – however many delegates felt that the virtual platform did reduce the chance for more in depth discussions that could have been possible in a face to face meeting.