ACT EU Multi-stakeholder Meeting on Decentralised Clinical Trials

1 SUMMARY

New and innovative clinical trial designs and methodologies provide various opportunities and challenges for the EU clinical trial environment. The EU decentralized clinical trials (DCT) project aims to address some of these challenges, in line with the European Medicines Agencies Network Strategy to 2025 and European Commission's Pharmaceutical Strategy for Europe. DCTs introduce new approaches to the conduct of clinical trials (CT) that aim to make them more easily accessible and convenient for participants to take part in, based on elements such as home health visits, direct-to-patient shipment of study drugs, and electronic informed consent.

The Accelerating Clinical Trials in the EU (ACT EU) initiative aims to develop the EU further as a competitive center for innovative clinical research. As one of the activities, The ACT EU Program held a multi-stakeholder workshop on DCTs on behalf of the EU DCT project, hosted by European Medicines Agency (EMA), on October 4th, 2022. The workshop has managed to bring together participants from all areas of the research community who shared perspectives.

1.1 Objectives

The intention was to get an overall picture of the EU DCT project group work of the European Medicines Regulatory Network on DCT collaboration, including the planned publication of a guidance paper on the use of decentralized elements in clinical trials in Q4 2022. Another aspect of the shared discussion was gaining a multi stakeholder's perspectives - specifically to bring forward the perspective of patient representatives and investigator site experts. The acquired knowledge should produce concrete recommendations for the upcoming guidelines and finally, a creation of a multi-stakeholder's platform in 2023.

1.2 Structure

The workshop took the form of a plenary session with breakout rooms and a panel discussion. The plenary session was facilitated by the core members of the EU DCT project team, consisting of clinical trial experts from the Clinical Trials Coordination Group (CTCG), ethical experts from the Commission Expert Group on Clinical Trials (CTEG), and Good Clinical Practice (GCP) inspectors from the Good Clinical Practice Inspectors Working Group (GCP IWG).

EMAs Executive Director *Emer Cooke* opened the workshop followed by remarks from The Head of the Pharmacovigilance and Epidemiology Department at the EMA, *Peter Arlett***,** and *Greet Musch* (FAMHP/CTCG). The opening remarks focused on emphasizing the importance of the project and the significance of DCT, especially in public health emergencies such as COVID-19, and how the use of the new technology influences the Clinical Trials (CT) landscape. The scope of the DCT collaboration across the European Medicines regulatory network was outlined by *Ditte Zerlang Christens*en (DKMA). There were 45 experts, among which 25 were onsite at the workshop. Besides the EU DCT project team, perspectives were incorporated from SAWP Scientific Advice Experts, MWP Data Methodology Experts, PDCO and Enpr- EMA Paediatric experts, PCWP Patient representatives, and HCPWP Health Care Professionals.

2 PERSPECTIVES

The next session has outlined the different perspectives of the involved stakeholders

2.1 Authority Perspective

2.1.1

The European Medicines regulatory network outlined the DCT recommendations, explaining the structure and the aim of guidance paper (an evolving document). The paper will focus on the decentralized elements in the conduct of clinical trials and the elements and roles of the "traditional CT" will not be repeated, as well as the GDPR-specific elements, unless it fits a purpose. The proposed Table of Content was also presented.

The general considerations in the DCT recommendation include the basic principle that the right, safety, and well-being of trial participants should be protected, as adherence to EU and national applicable laws, regulations, and established standards for CT.
The involvement of patients and investigators in an early and sustained manner is important to be able to answer their needs. Moreover, a trial-specific rationale where any transfer of burden to trial participants or investigators, should be weighed against the benefits of using decentralized elements. Therefore, a specific risk-benefit assessment is one of the main points of the recommendations.

Additional considerations pinpoint the need for appropriate training of all involved, qualifications of the third parties performing trial-related tasks, generating reliable and robust data, and finally, development of IT devices/technologies to fit the purpose.
A contingency plan should be in place to minimize any risk.

2.1.2 Clinical Trials Oversight: roles and responsibilities

The DCT process is characterized by fewer on-site visits, while the involvement of the third parties, use of E-Systems, and amount of incoming data (wearables, home nursing staff, the patient-reported outcomes, etc.) increase. More tasks are being delegated, but the responsibilities stay the same. Therefore, it should be ensured that the sponsor and the investigator keep oversight of the safety. They should document the conducted time and place and by whom are the tasks conducted. Additionally, a clear communication plan between the different parties is needed and procedures must be in place to handle the consistent flow of information.

2.1.3 Informed Consent Process

The process can involve risk-based approach hybrid forms such as informed consent interview (remote or on-site), considering the importance of face-to-face (video call), leaflet containing patient information (digital, paper or video), taking into consideration the technological preference, and signature (DCT recommendations electronic or wet ink), depending on the national legislation.

2.1.4 Delivery of medical Products, administration, and procedures at home'

The process of delivery was explained as follows: from the sponsor to the participant's home, from the pharmacy to the investigator's site, and from a local pharmacy (close to the patient's home).

The focus should stay on trial-related procedures performed at the trial participant's home by site personnel, third party, or trial participant, by taking into consideration the feasibility of the procedure, the impact on the trial participant-investigator relationship with fewer on-site visits, the need for on-site visits or visits at home and the provision of devices by the sponsor to capture data.

2.1.5 Defining and handling source data and remote monitoring

The authority perspective finished with the current focus of the source data- raising awareness of the increased percentage of collected data outside the CT site, and the increased complexity of data flow. The same principles stay in force no matter the data location, and it is the sponsor's responsibility to ensure that the investigator has control and access to source data. Remote monitoring was tackled only as a work in progress, but it remains an important process to follow.

2.2 Sponsor and CRO Perspective

2.2.1 Industry sponsor perspective: Opportunities and challenges for the use of DCT elements in clinical trials - Alison Bond (EFPIA)

The representative from the industry emphasized that the selection of DCT elements depends on the trial design and participant population. They framed the elements in several categories: Telemedicine; Mobile Healthcare Providers; Local Healthcare Providers; Local laboratories; and Imaging Centers; Direct to Participant IMP Shipment and Administration; Electronic Informed Consent; Concierge Services; and Digital Health Technologies.

The industry sees opportunities for enhancement of the research through DCT approaches in several aspects: to remove the geographical barriers; the potential to increase the diversity of the trial participants; reduce the burden of participants and caregivers; empower the participants with choice and facilitate innovation by using novel technologies and digital health.

On the other hand, the industry has perceived and already experienced some challenges in several areas:

1. *Operational and Technology:* such as data consolidation, the complexity of data flow, the potential for a selection bias, and impact on existing operations.
2. *Relationships and oversight*: starting with the relationship between the investigator and sponsor, and the investigator's oversight of patients and distributed care team. There is a challenge in reporting and handling the potential AEs/SAEs and the site training and acceptance of the use of DCT trial elements in general.
3. *Data Privacy/ protection:* with participants names and addresses in platforms and the electronic signatures.
4. *Data Quality:* comparability of data for site and remote assessments and data acceptability and management of large data.
5. *Regulatory Framework challenges:* lack of regulatory guidance and fragmentation and adaptation according to local regulations.

2.2.2 Academic Sponsor perspective: Experiences on use of DCT elements during covid-19- Vassilis Golfinopoulos (EORTC)

The representative from an academic spin-off company that works with oncology products showcased several aspects of using DCT elements during the pandemic. First, they emphasized how any DCT elements were triggered by the sites and needed centralized oversight such as centralization of COVID-19 related communication, early sponsor assessment of COVID-19 impacts on current and future trials, as well as clear communication to investigators and the site staff on COVID-19 measures.

The informed consent has been taken remotely by request, while initial consent has been taken on-site. The imaging exams have been done at a remote site by preference unless imaging must have (as per protocol) been done at the main site when imaging results drive treatment allocation.

The patient visits have been allowed to be switched to remote, such as phone visits. The standard repeated assessments could be done by contracted laboratories. The study treatment has also been delivered to the patient's home by request. Additional consent for drug shipment to the patient's home has been provided too. The experience from this company pinpoints the fact that direct-to-patient delivery needs work for each case. The presentation continued with an overview of the example of one member state who had incorporated DCT elements during the pandemic, concluding that: the COVID-19 measures that have a significant impact on the protection and safety of the involved patients were put in place of Urgent Safety Measures, and the traditional measures were submitted as an appendix to the protocol of the regulatory bodies. Moreover, the impact of the pandemic was seen in all hospitals, no matter the size, while the pharmacies kept open allowing drug reception. The results were home IMP shipment to patients in 7 studies, remote visits, and use of the local laboratories. The monitoring on site has been put on hold with follow-ups with the site by phone. The source data verification has not been in place, and the treatment has been dispatched to the patients abroad if unable to travel to the country.

The main point of the presentation was that in oncology, they are not yet ready for fully remote procedures, but rather some hybrid forms. According to their experience, the decentralized processes come on top of the existing ones, and what is paramount, they require different setups in different member states.

2.2.3 CRO Insights and Experiences: How to solve identified challenges on the implementation of DCT elements in clinical research- Yoanni Th. Matsakis (EUCROF) Fiona Maini (ACRO)

The first CROs viewpoint focuses on three main points of consideration: Patient safety; data protection; and quality of data. First, regulatory harmonization is needed for the DCT elements that are implementable in some countries and jurisdictions, but not in others. The CRO representatives have raised this question addressing the need for this aspect to be implemented into the recommendations, and how the harmonization will be optimally done. They also made a point if it would be possible to deploy traditional /in-person approaches under the same protocol in countries where the DCT elements are not deployable. Topic number two described the importance of site readiness such as the implementation of multiple sponsors with multiple technologies, some technologies may be site dependent: EMR; telehealth visit systems; etc., and the sites may require upgrades from

an organizational and technical standpoint. The questions that arose were: Interoperability between CR systems and HIS Software and how to handle DPIA in certain situations?

Data protection as topic number three pinpointed the GDPR as being perceived as an "inhibitor" for the adoption of innovation. The CROs view this as an innovative regulation that shall facilitate the adoption of technologies and organizational innovations for DCTS. Other topics for further discussion cover the protocol fiscalization / hybrid situations for example if there is any way from the regulatory viewpoint to allow patients to change in-person versus remote visits during DCT randomly or must patients commit to one way? Additionally, can differences in the adoption of DCt tools and methods among sites be allowed in the same trial? Another consideration addresses the responsibility and role of the local HC providers versus DCT personnel pinpointing the need for a detailed role and responsibilities assessment to be made.

The second presenter introduced the DCT WP Tool kit and outlined the key learnings and recommendations for the acceleration of the DCT in the EU. First, they emphasized that DTC is not a new concept, because the DTC and the technologies are established. There are many Case Studies, lessons learned, recommendations, and training tools to help inform the EU DCT Recommendations. Second, it is paramount that the variability is recognized across the Member States. For example, there are variations in the national legislation provisions, regulations, and guidance on key DTC and tools. Enabling transparency of Member State requirements is also one of the recommendations. The development of a central repository of national legislation, regulation, and guidance would mitigate challenges for sponsors and CROs in trying to execute pan-European DCT. Finally, enabling greater coordination across regulatory agencies would help advance DTC.

2.3 Patient and Investigator Perspective

Hybrid solutions were the main point of the presentation of the patient's viewpoint, enhancing the importance of the possibility to have a choice as a patient. The hybrid solutions would be a good fit for the less complex trials that do not require in-person visits (vital signs, EKGs, etc). The data in that case is collected via tele-healthcare, remote data collection, or direct-to-patient supply. The hybrid model can be a good solution for fewer complex trials that require in-person visits (injections) conducted via mobile clinicians or alternative sites (mobile clinics, retail sites). The hybrid model can in some instances be a good solution for complex trials (complex screening, protocols, cell therapy, MRI) conducted via research sites (academic medical centers) or local hospitals. Other points were that decentralization can lower motivation if it is forced, and it can be an issue for people with low technical skills and sometimes even the physicians' technical skills can be a barrier. When it comes to data privacy, they explain that decentralization means patient data transfer and custody on digital access, which is underestimated for most of the projects. They offered a solution, such as PIA (Privacy Impact Assessment) done by a data security company. It is important, from the patient's perspective that the patient remans the owner of the data and that the data should go back to the patient after CT is done.

The investigator's perspective outlined the patient's opinion survey during COVID-19 about the DCTs, where the result is that 66 percent of patients must travel for more than 30 minutes to reach the Center where the clinical research is made that can be hurdle. 73 percent of patients were interested to be reached at home for visits during CT. From 50-61 percent of patients deemed important the following: biological sample at home

and delivery of the medications at home. The conclusions are that the DCT is quite a new modality to conduct trials and they are still a small percentage of the volume of studies and trials. They are evolving and are an important step in the field of clinical research. They are particularly useful for patients with rare diseases for whom the referral can be very distant and not easily reachable, for patients with limited mobility, and/or functional disability and that are not autonomous. It is paramount to find a balance between the patient's needs and the healthcare professional's workflow. Identification of adequate and secure electronic platforms is also needed. Additionally, adequate training on the platforms for investigators and patients is crucial before starting the trial.

2.3.1

Panel discussion to explore patient and investigator site perspective.
Panelists: Sally Hofmeister (World Duchenne Organization) Julián Isla (COMP and Dravet Europe) Aisling Walsh (EFCNI) Mira Zuidgeest (trials@home) Dr. Filippo Pieralli (University Hospital Careggi) Dr. Francisco Bautista (Princess Máxima)
Moderator: Kasper Bendix Johnsen (Danish National Center for Ethics)

The panel discussion revolved around the relationship between the investigator and the patient as a key aspect, asking the question if a meaningful relationship would be possible with fully DCT. The relationship brings trust, and that is crucial according to all the panelists. Consequently, at least one face-to-face meeting with the investigator is inevitable. Another aspect for the panelist was the flexibility and the possibility of co-creation of the process to be beneficial for all involved in the trials. They agreed that this interaction would be the best at the beginning of the CT and that the follow-ups could use elements of full DCT procedures. Informed consent was brought up as another crucial point. The technical logistic was also mentioned, in terms of simplifying the whole process. For example, bringing the patient's device could alleviate the process. Lastly, attention was brought up to the potential "elephant in the room", for example, the investigator's bias in some instances. They all agreed that it is in the best interest how DCT can be beneficial for patients and the process should drive forward to see if hybrid or fully remote DCT can be most useful. They emphasized that despite the opportunity to try out the fully DC process, this may not be the future for all types of clinical trials.

3 CONCLUSIONS

The workshop has managed to gather different stakeholders and to gain insights and perspectives, to proceed with future deliverables, such as the recommendations-guidelines paper in Q4 2022, and the creation of a multi-stakeholder platform in 2023. The world of CT is rapidly changing, and DCT is here to stay. The experiences pinpoint the ultimate goal – a harmonization on the EU level to facilitate large CT to develop the EU further as a competitive center for innovative clinical research. The main logistical challenges leveraged by most of the involved stakeholders point to the need for balance between patient needs and the investigator, the possible hybrid models, the right technological development and training, data protection harmonization, and "one model does not fit all". Therefore, a possibility of a choice, the specificity of the diseases and the target patient group to decide which model of CT to use is something to consider in the future expansion.