Bringing the Trial to the Patient by Leveraging Electronic Technology

Decentralised 'virtual' clinical trials in oncology are becoming the 'new normal' with the help of technology, but patient-centricity needs to remain the focus in this changing climate

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Clinical research has been regionally disrupted in the past by natural disasters, e.g., hurricanes, wildfires, and tsunamis (1-2). Isolated disease outbreaks have caused studies in countries around the world to experience temporary, but critical, interruptions. The extent of worldwide disruption caused by the COVID-19 pandemic is unprecedented in the modern era of regulated clinical research. The economic fallout of the pandemic has far-reaching consequences for R&D sponsors and CROs, as well as investigative sites and regulatory authorities. In oncology trials, the impact of this disruption is amplified even more because of the nature of oncology protocol designs that often require strict cycles of standard of care (SOC) in addition to investigative treatment. Further, the assessment of tumour progression or response could involve numerous visits to implement sophisticated imaging or other modalities. Other affected clinical trial operations include the supply chain, participant recruitment and retention, and laboratory kit supplies – especially in oncology studies. The medical infrastructure within which cancer patients receive care and take part in clinical trials is increasingly challenged with the influx of COVID-19 patients. Finally, the worldwide global pandemic is nowhere near finished, and, therefore, all hands are on deck to meet these challenges and assure the continued safety and support of oncology clinical trial participants.

All aspects of clinical research, especially oncology, are feeling the impact of COVID-19 as seen in **Figure 1**.

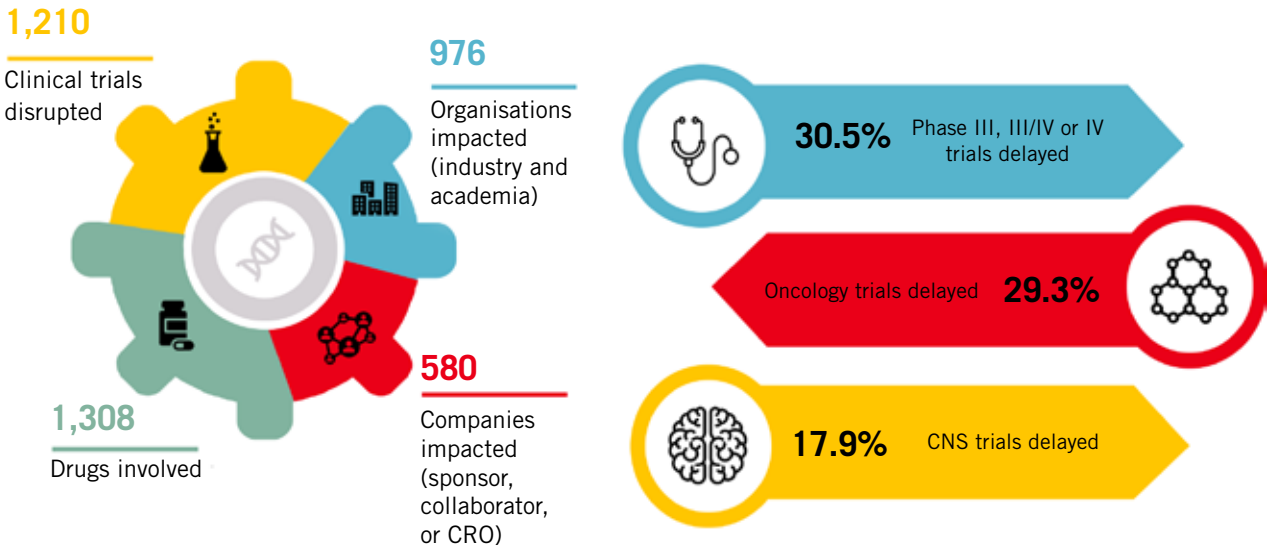

Figure 1: COVID-19 impact within clinical research (adapted from (3))

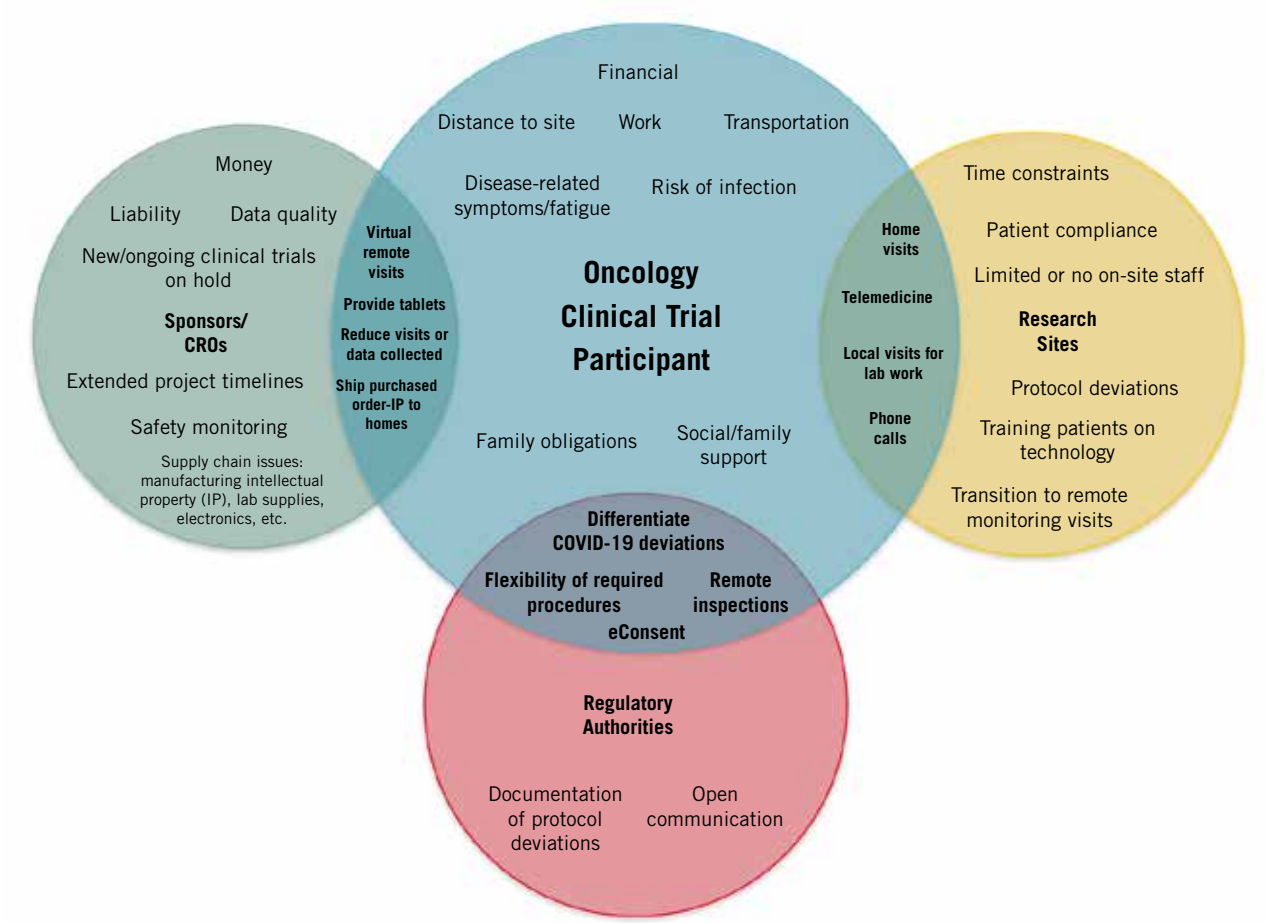

Figure 2: Challenges and proposed solutions to oncology clinical trial participants in the COVID-19 era

On 25 June 2020, Global Data demonstrated that 1,210 clinical trials have reported disruption, involving 1,308 drugs in development, with 29.3% of these in the realm of oncology clinical trials (3). These delays may affect launches for new studies, screening and/or enrolment in ongoing trials, and/or research-only visits being placed on hold while reconfiguring operations. Major clinical operations are critically affected, requiring the urgent development of logistical solutions for the supply chain dysfunction and shortages of materials and resources, including personnel to produce investigational product, as well as lab kit supplies required for collection of protocol mandated lab samples. Complicated specialty lab procedures and exploratory study endpoints may also be forfeited in lieu of safety lab samples that can be collected in local labs in geographic proximity to clinical trial participants.

A cancer diagnosis is a cataclysmic life event. With the patient in focus, clinical staff must manage a wave of support to engage multi-level personnel through all clinical stages including initial surgery/diagnosis, SOC, investigational therapeutics, and safety surveillance. Last year, when things were 'normal', oncology clinical trial participants still faced formidable barriers to clinical trial participation. When an individual with cancer gives consent to take part in a research study, they agree to accept personal sacrifices. Additional burdens, concerns, and personal considerations may include, but are not limited to: insurance coverage, finances, work schedules, possible loss of job and income, home responsibilities including child and/or elder care, geographical distance from the research centre, ability to travel, disease-related symptoms, and frequent significant fatigue. Since the start of the pandemic, the weight of these concerns on clinical staff has steadily increased, along with a heightened concern for infection secondary to treatment-related immunosuppression. The ability of investigators, sponsors, and CROs to tailor methods and procedures to permit studies to continue safely, while complying with changing regulatory authority guidance, became a priority all at once (4).

In the past, the incorporation of patient-facing technology within clinical research has elicited theoretical intrigue; however, the endless possibilities have never been fully explored (5). Technology has now moved into the forefront in the effort to bring the clinical trial to the patient. Some of the terms in use may be ambiguous, beginning with 'virtual clinical trial'. Other terms used to define trials using patient-facing technologies to limit on-site visits are decentralised trials, remote trials, 'direct-to-patient', and hybrid trials. Regulatory authorities, such

as the FDA may only consider a trial 'virtual' if it involves no humans.

Definitions are evolving within the context of the global pandemic. The preferred term for such trials remains under discussion; however, the term 'decentralised' seems to be the most widely accepted. Decentralising trial functions are implemented in order to retain as much of the structural framework of the study design (e.g., endpoints, assessments, etc.) as possible while protecting the health and safety of the participant (6).

The use of patient-facing solutions in clinical research such as electronic clinical outcome assessment systems, biometric devices, along with applications on cellphones, allow for quality data collection to continue during the transition into the 'new normal' (5). Virtual reality is being piloted as a tool to support remote clinical trial activities (7). In studies where technology is integrated into the design, the information on treatment effectiveness can be collected via electronic questionnaires, assessments, diaries, and wearable trackers and sensors from which data funnel into the site from remote locations. Patient-facing technologies and telemedicine portals are preventing many studies from coming to a complete halt by acting as a 'release valve'. For example, electronic patient reported outcomes (ePRO) platforms as a replacement for paper patient diaries have become an established norm. Likewise, tablets or cellphones are being integrated for use instead of paper for the collection of participant-completed questionnaires and assessments. In this COVID-19 new world order, 'e' for 'electronic' is the new gold standard with the rise of eSource in a wide variety of ePRO technology, electronic case report forms tied to electronic data capture, interactive web response systems, interactive voice response systems, electronic medical record, electronic trial master files, and electronic consent systems, to name a few.

Compliance with existing clinical research laws and regulations is ongoing during pandemic shutdowns and lockdowns. Therefore, as the need for flexibility in protocol implementation increases, regulations and policies are adapting to meet the demands of clinical trials worldwide. Researchers and regulatory officials are working vigorously to develop and implement these changes, while sites and sponsors/CROs are providing critical devices and digital applications while adhering to regulatory, privacy law(s), and guidance for each country.

Telemedicine
Alternative location for assessment (e.g., local providers, home visits, etc.)
Reduced site visits
Remote EMR-uploading of redacted source to secure file transfer platform
Shipping oral investigational drugs direct to study participants
Remote study monitoring visits
Risk-based monitoring

Table 1: Technologies/strategies used or planned for use in oncology clinical trial assessments

Regulatory authorities (e.g., FDA, EMA, MHRA) rapidly responded to the state of emergency via guidance to present the current thinking on compliance in the time of the pandemic. The FDA suspended the review and comment period for its *FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency*. A dedicated email address is provided for direct access to answers pertaining to the pandemic. The guidance contains an extensive question and answer section. The key words are: communicate, designate, document, and annotate. Sponsors are repeatedly urged to contact their assigned FDA review division, Institutional Review Board and, if applicable, the Data Monitoring Committee for each study and to document this communication.

Protocol deviations are to be designated by cause to COVID-19 with documentation of deviations, which then must be annotated in the final study report with the reason why COVID-19 caused the deviation (8). EMA issued *Guidance on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic Version 3*, addressing similar clinical trial continuity issues (9). The MHRA released *Advice for Management of Clinical trials in relation to Coronavirus* (10).

Along with safety of trial participants, the protection of privacy is of the utmost concern. The IT regulatory requirements for electronic systems implemented, including electronic signatures, continue to remain in effect. Privacy regulations around the globe, including GDPR in the EU, Personal Information Protection and Electronic Documents Act in Canada, the Health Insurance Portability and Accountability Act in the US, Cybersecurity Law in China, and Australia's Privacy Act all provide the structure required to safeguard personal information moving from investigative sites to sponsors/CROs for remote monitoring. Secure file transfer solutions are necessary to provide a protected point of information transfer.

Although the pandemic is believed to be in the early stages, a concerted effort is ongoing worldwide to better understand the impact of change. A combination of surveys and interviews of oncology investigators worldwide were conducted by IQVIA (formerly Quintiles and IMS Health, Inc.) and the Cancer Research Institute in March and April of this year. The dataset is derived from the IQVIA database and ClinicalTrials.gov on oncology clinical trials of 36 investigators conducting clinical trials around the world. The combined surveys/interviews revealed interesting international comparisons. The investigation found that active oncology trials conducted in the US and Europe were negatively affected by the pandemic, with most centres

experiencing a significant reduction in the rate of enrolment. Oncology trials conducted in Asia, however, showed that most centres did not experience reduction in enrolment. The type of investigational cancer therapy and route of administration were key determinants of negative impact caused by the pandemic. Intravenous formulations requiring infusion posed the greatest logistical challenge, second only to intratumoural administration. Patient safety concerns resulted in a risk-benefit analysis reported by investigators in the interview for ongoing trials with safety at the forefront (11). In another limited dataset, Waterhouse *et al* reported on the results of a survey conducted in late March 2020 of clinical programmes exploring the impact of the COVID-19 pandemic on oncology clinical trials (12). The survey was distributed to clinical programmes affiliated with American Society of Clinical Oncology committees, steering groups, and task forces; 32 responded to the survey with a nearly equal distribution between academic and community-based programmes. Most respondents reported that their organisations had implemented formal policies tailored to meeting the demands of the pandemic including remote patient care interactions, patient review of symptoms and telemedicine visits. For 75% of the respondents, the majority mandated remote work by research staff, remote study initiation visits, and remote monitoring by sponsors and/or the CRO.

As the need for e-technology continues to increase, it is imperative that researchers and developers keep in mind the study endpoints but also the capabilities and satisfaction of the users of the device. User-friendly technology will assist in patient enrolment and protocol adherence within oncology clinical trials as data entry and monitoring occur simultaneously, instead of only at or prior to periodic visits (13). While this may be the case, these e-devices and apps must meet the regulatory and privacy requirements of each country. Current regulatory guidelines will continue to be updated as the innovations created by including e-technology into protocol study designs will likely outlive the pandemic. By adapting user-friendly applications and e-devices in oncology protocols, clinical trials become more accessible and patient-centric as the weight of participating in the trial is more equally distributed between the patient, the site, and sponsor/CRO personnel.

References

1. *Flory K* et al, *Clinical research after catastrophic disasters: Lessons learned from hurricane Katrina,* Prof Psychol Res Pr *39(1): pp107-12, 2008*
2. *Kardinal CG, Hurricane Katrina: The challenge to cancer clinical research.* Ochsner J *6(1): p38, 2006*
3. *Visit: www.globaldata.com/covid-19*
4. *Jiang DM* et al, *Transitioning to a new normal in the post-COVID era,* Curr Oncol Rep *22(7): p73, 2020*
5. *Polhemus AM* et al, *Accelerating adoption of patient-facing technologies in clinical trials: A pharmaceutical industry perspective on opportunities and challenges,* Ther Innov Regul Sci *53(1): pp8-24, 2019*
6. *Visit: www.clinicalleader.com/doc/what-exactly-is-a-virtual-clinical-trial-0001*
7. *Persky S, A virtual home for the virtual clinical trial,* J Med Internet Res *22(1): e15582, 2020*
8. *Visit: www.fda.gov/regulatory-information/search-fdaguidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency*
9. *Visit: www.ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf*
10. *Visit: www.gov.uk/government/collections/mhra-guidance-on-coronavirus-covid-19*
11. *Upadhaya S* et al, *Impact of COVID-19 on oncology clinical trials,* Nature Reviews Drug Discovery *19(1): pp376-7, 2020*
12. *Waterhouse DM* et al, *Early impact of COVID-19 on the conduct of oncology clinical trials and long-term opportunities for transformation: findings from an American Society of Clinical Oncology survey,* JCO Oncol Pract *[ePub ahead of print]: OP2000275, 2020*
13. *Vogel MM* et al, *mHealth and application technology supporting clinical trials: Today's limitations and future perspective of smartRCTs,* Front Oncol *7: p37, 2017*

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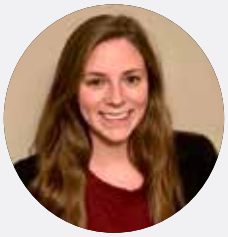

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