

Clinical research disruption in the post-COVID-19 era: will the pandemic lead to change?



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The unprecedented situation we are facing has strongly disrupted the clinical research rules. Nevertheless, for the scientific community, it may represent the opportunity to learn important lessons. The COVID-19 pandemic suggests that it is possible to alleviate redundancy in clinical trials, and while preserving the rigour of a study, can offer a new, less burdened and more inclusive vision of clinical research for the scientific community of tomorrow. This perspective article describes clinicians' vision of how the pandemic could change the roles of clinical research.

Since the beginning of the SARS-COV2 outbreak in Wuhan, more than 24 million people have been infected all around the world and more than 800 000 have died from the disease so far. In this scenario, Europe is facing one of the worst crises that our National Health Systems have ever encountered in the last 50 years. Six months after the first COVID-19 diagnosis, the lockdown is being eased in European countries and our lives are slowly adapting to 'a new normality'.

Providing care to immunocompromised patients with cancer during this pandemic has been extremely challenging and oncologists face many challenges in providing cancer care during the COVID-19 outbreak. Data from China reported that patients with cancer who are infected with COVID-19 are at 3.5 times the risk of requiring mechanical ventilation or intensive care unit (ICU) admission, compared with the general population.¹ Additionally, the limitation of resources in outpatient settings, including administrative staff and specialists, has hindered the routine care of patients.² National and international cancer societies published priority-driven guidelines for the management of oncohaematological patients on therapy during the COVID-19 pandemic and recommended considering

treatment delays and modifications on a case-by-case basis, taking into account the characteristics of the patient and the disease.³ In addition to routine patient care, the imperative of reducing the number of non-urgent visits to the hospitals, which characterised the last 6 months, had implications for research institutions performing clinical trials. An Italian survey of medical oncologists reported that both clinical research and scientific activities were reduced in over 80% of respondents.⁴

Although conversion to telemedicine has maintained the continuity of care for many patients, the COVID-19 pandemic has massively disrupted clinical research and many cancer centres halted clinical trial activities including patient recruitment.

Regulatory Agencies have disseminated extraordinary measures to guide healthcare workers to continue clinical trials ensuring patient safety and maintaining data quality. The implementation of these measures has helped mitigate the negative effects of the pandemic on the clinical research field (https://ec.europa.eu/health/sites/health/files/files/eudralex/vol10/guidanceclinical_trials_covid19_en.pdf).

Hospitals have needed to prioritise clinical activities managing patients and staff suffering from COVID-19. Therefore, carrying out clinical trials according to the rigid interpretation of GCP-ICH (Good clinical practices–International Conference on Harmonisation) rules was not always practically feasible. As we adapt to 'the new normal', there is a feeling among some healthcare workers that the important lessons learnt during the pandemics will disappear with the end of the emergency phase.

In the field of clinical research in oncology, for instance, we learnt that a reasonable balance can be achieved between maintaining the scientific integrity of the study, patient safety and regulatory burden. During the



COVID-19 era, both individual researchers and research organisations have realised that there is a different way of delivering clinical research and that ‘flexibility’ and ‘altruism’, which have been keywords of the COVID-19 era, may represent one of the legacies as we move forward within the post-COVID-19 world.

Practical solutions used during the pandemic that merit the consideration of long-term implementation in clinical research include the following.

1. Telemedicine: the COVID-19 pandemic led to an unprecedented change in clinical operations, motivating physicians and healthcare systems worldwide to rapidly implement telemedicine programmes to reduce or replace in-person visits and to allow workforce sustainability and staffing.⁵ Before the pandemic, telemedicine was underused while actually, it is quickly becoming the preferred mode of delivering care for patients with cancer including follow-up, on-treatment and second opinion consultations. When asked about the perception of safety to attend research visits ‘remotely’ or in-person, half of clinical trial participants preferred phone visits⁶ or telehealth that is enhanced by face-to-face communication.⁷ A 2015 Cochrane review examined the impact of telemedicine involving remote monitoring compared with in-person or telephone visits for chronic conditions, including diabetes and heart failures, and found similar health outcomes.⁸ Larson *et al*⁹ showed that telemedical intervention in patients with cancer is comparable with face-to-face interaction meetings regarding the quality of life but no data exist about the oncological outcome in patients who received telemedical advice. These measures, although necessary in the context of the pandemic, serve as an opportunity to reconsider the utility of frequent in-person hospital visits for patients enrolled in clinical trials, particularly when the therapeutic is an oral drug that can be delivered by courier service. Moreover, less than 5% of cancer clinical trials adequately accrue ethnic minorities (OR 0.7 with respect to white patients in cancer clinical trials)¹⁰ and a potential explanation is that travel burden to centres mandated by specific trials (eg, rare cancers) implies time off from work and family commitments for both patients and careers leading to financial repercussions.¹¹ Therefore, reducing the frequency of in-person visits could potentially increase access to clinical trials participation and diversity in recruitment. At present, several activities can be potentially provided by electronic tools (informed consent discussion and signature, medical history collection focused on addressing eligibility criteria during the screening procedures, evaluation of the quality of life and safety with electronic Patient Reported Outcome (ePRO)) and this could be permanently accepted in clinical trials procedures. The implementation of telemedicine requires funding, user guidelines, data protection integrity and management of reimbursement policies. Lack of privacy and security standards plays an important role in the legal challenges

facing telemedicine and may have considerable implications for the acceptance of telemedicine services.¹² Moreover, the relationship between telemedicine reimbursement rules and access to care is complex; although the COVID-19 pandemic has certainly brought increased coverage for telemedicine services, nationwide standardisation of payment policies is still lacking.¹³ With the second-largest burden of COVID-19 in the world, for instance, Italy does not currently include telemedicine in the essential levels of care granted to all citizens within the National Health Service and no formal input was given on telemedicine by health authorities, despite high pressure on health services during the first phase of the epidemic. However, the time has arrived to change this situation, and experts from different fields should work together on this important issue.

2. Remote monitoring visits: given the pandemic, alternative mechanisms of oversight and monitoring have been implemented including remote monitoring. Local data protection policies in many parts of Europe often precludes the remote source data verification (eg, providing the sponsor with copies or remote access to electronic medical records). It is evident that such a model cannot work alone, nevertheless, a mixed (on-site and remote), risk-based model that takes into consideration national and local restrictions and the urgency of source data verification can be permanently implemented in the new research organisational model. Remote monitoring for some clinical trials is feasible and cost saving for the sponsor. This may be particularly relevant for academic-sponsored trials, given that on-site monitoring can account for about 20% of the total trial budget.¹⁴
3. Laboratory tests: during the pandemic, when it was not feasible for patients to travel to the clinical trial centre, it was acceptable that blood tests, imaging or other diagnostic tests were done at a closer local facility provided it is certified as per national requirements. The ability for tests to be carried out outside of the trial centre perhaps should be continued and integrated into clinical trial procedures—at least for some safety blood tests that do not represent the primary endpoint of the trial, and for radiological tests when a centralised evaluation (Blinded Independent Central review (BICR)) is planned for progression-free survival end point analysis, or when overall survival is the main objective of the study. Moreover, as a general strategy, methods and frequencies of safety assessments should be rationally determined in trial protocols taking into account preclinical and clinical safety data, be scientifically and ethically justified and balanced with the risks associated with hospital visits.¹⁵ Finally, the issue of funding needs to be addressed and the cost of these extra hospitals’ procedures need to be traced and reimbursed to the laboratories providing the procedures by the sponsor. This may be easier if research networks are established and oncologists and radiologists of pe-

ripheral centres are trained as subinvestigators with delegated duties under the supervision of the main study team.¹⁵

4. Ethical Committee (EC) evaluation: the Italian situation. In Italy, there are 90 ECs actively evaluating trials and the median lead time between clinical trial application (CTA) submission and the site initiation visit (SIV) is 202 days (median EC evaluation time 152 days). Other studies report even longer duration reaching up to 10–12 months for the whole process of trial activation.¹⁶ During the emergency, AIFA (Italian Medical Agency) appointed a unique EC for evaluating all COVID-19 interventional studies and this dramatically reduced the time of approval (about 30 days between CTA and SIV). The outstanding lesson we learnt is that is it not more deferrable the brave decision to identify a single EC for trial (or at least for the area) to speed up the process of approval, particularly when looking at the upcoming implementation of the European Portal for CTA submission that imposes the identification of a central EC and defines strict times for evaluation. When the ClinicalTrials Directive (EUCTD) adopted in 2001 to facilitate and improve clinical research within Europe is strictly followed, the median approval duration is 59 days.¹⁷ Lastly, a simplification of approval procedures may translate in a significant reduction of the costs of submission: a Swiss trial reported a median time of 49 days and a median cost of 72.000 dollars for the submission preparation of a randomised clinical trial to the authorities.¹⁸
5. Contract negotiation: the example of the tocilizumab trial. Community-based research programmes face many barriers to participation in clinical trials, and research contract and budget negotiations have been consistently identified as time-consuming procedures and a barrier to study participation. American Society of Clinical Oncology's (ASCO) Community Research Forum conducted a survey about specific challenges in clinical research among 780 clinicians: 77% of the respondents acknowledged barriers in the process of trial activation in terms of budget negotiation and legal review.¹⁹ After the publication of the survey, ASCO recommended the standardisation of negotiation processes and the creation of contract templates as necessary tools to implement the trial activation process.¹⁹ During the pandemic, the National Cancer Institute of Naples promoted a therapeutic trial with tocilizumab in patients with COVID-19. The drug was supplied free of charge by the drug company, an electronic CRF for data entry and drug order was created on the web system of the coordinating centre assuring drug delivery in 24 hours, and a single contract was signed between Agenzia Italiana del Farmaco (AIFA) and industry without any administrative acts required at peripheral centres. The fortuitous combinations of all these facilities translated in the opening of 600 centres in less than 3 weeks. Aside from the exceptional circumstances of a trial using a drug reducing ICU necessity during the emergency, this model suggests that the obligatory implementation of a national contract template, with an agreed line listing activity costs and minimal local negotiations to meet hospital requirements, could dramatically speed up the global process of contracts leading to a faster opening of clinical trials and access for patients. The velocity in trial activation is not an obvious guarantee of trial success in terms of results (Actemra/RoActemra phase 3 trial in hospitalized patients with Covid-19 associated pneumonia (COVACTA) trial is a clear example of this) but undoubtedly contribute to the efficiency of the system and would be beneficial to all interested stakeholders, including industry sponsors, the research sites and the patients who may ultimately benefit from participation in clinical cancer research.
6. Remote regulation audits: regulatory audits sponsored by the authorities are essential to confirm the quality and veracity of clinical data before placing a new molecule or new strategy at the disposal of patients. These on-site audits generally take an enormous amount of preparation time, an attendance time that varies from 3 to 5 full days and mobilises in addition to government personnel, local teams and sponsor teams over many weeks. Again, the remote visits and remote controls as set up for certain studies during confinement could be an additional added value in the optimal organisation of tomorrow.
7. Data sharing and generosity: the example of the TERAVOLT (Thoracic Cancers International COVID-19 Collaboration) registry. The idea to collect data on mortality and disease outcome in patients with lung cancer affected by COVID-19 was launched in March 2020 with a simple email immediately spread among the international community involved in lung cancer treatment, after the Chinese warning that the fatality rate in patients with lung cancer was higher than in other tumours. The TERAVOLT registry involved 21 countries worldwide and was endorsed by a number of international oncology societies and physicians who accepted to collect and share data without any form of financial support.²⁰ In less than a month, data on 200 patients were collected and analysed, and actually, more than 400 patients have been registered in the eCRF. The scientific community realised that, aside from individualism and personal academic glory, the necessity to collect data to take better care of patients with lung cancer was a priority and responded promptly. In the era of big data and learning machines, the generous and altruistic sharing of knowledge and data, could represent an unimaginable step forward and an unprecedented turning-point in the treatment of cancer.
8. Meetings: during the COVID-19 era, the majority of research conferences have been cancelled or postponed on an unparalleled scale, and attendance at confirmed meetings is likely to be lower than expected due to the fear of the disease. Basically, all the international



congress that took place in the last 4 months as ASCO, ESMO breast, AACR and Society of Gynecologic Oncology (SGO) were performed remotely and represented a great success with more people attendant remotely than on-site, reduced time away from the hospital for the physicians, less cost and carbon footprint. Nevertheless, besides the current emphasis on online formats, we must honestly recognise that about half of the global population has no internet connectivity.²¹ It is time for the global scientific community to recognise the challenges that our less fortunate colleagues regularly face and capture this exceptional opportunity to build a more equitable global community for the scientists of tomorrow.

CONCLUSION

This pandemic has represented an unparalleled threat for all of us, but also a tremendous opportunity for gaining a new vision in the world of clinical research. COVID-19 has pointed out that sometimes, high level of bureaucracy in research rules place unnecessary burdens on patients and clinicians and it suggests that it is time to alleviate bureaucracy and introduce some practical changes into research organisation that will possibly promote patient access to trials and reduce the costs of the clinical research. Nevertheless, it is of utmost importance to underline that bureaucracy alleviation does not mean laxity with dramatic consequences on the quality and consistency of clinical research and a careful balance needs to be maintained between the simplification of the procedures and the reliability of data.

Moreover, it is time to remember to ourselves that it is patient care, not personal glory, that provides a sense of meaning in our roles, and to reconsider a more generous approach in sharing information with colleagues in order to build a robust scientific community of tomorrow.²²

Given that the pandemic and its consequences are unlikely to dissipate soon, the time is arrived to fundamentally rethink study designs and procedures in order to optimise clinical cancer research. Moreover, robust adaptations could make the field more resilient to future pandemics. The extent to which changes should be implemented will vary by trial type and phase and although it could be easier to maximise translatability to routine practice for a phase III trial with a standard arm comparator, it would be more challenging for a first in the human study with new class agents.¹⁵

All these relevant changes will require a profound renewal of our tight global structures. However, if we have the will to have all innovative changes in place in a proper time frame and sharing a common vision and mission on research, then we will be creating a new era in clinical research. The WHO has encouraged all of us to think innovatively²³ and as Walter Disney said ‘if you can dream it, you can do it’.

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