Managing oncology clinical trials during COVID-19 pandemic

Roberto J. Arai a,*, Camila M.V. Moniz a, b, André T.C. Chen a, Milena P. Mak a, b, Roger Chammas a, Paulo M. Hoff a, b

a Instituto do Câncer do Estado de São Paulo - ICB, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Brasil
b Instituto O’Or de Pesquisa e Ensino - IDOR, São Paulo, Brasil

ARTICLE INFO

Keywords:
Oncoclinical trials
COVID-19

ABSTRACT

São Paulo city is the epicenter of the Brazilian COVID-19 pandemic. The Instituto do Câncer do Estado de São Paulo is currently conducting 161 multinational sponsored trials plus 116 in house studies in the oncologic population. There are 242 currently active participants and 180 patients in follow-up. The management of the tightly controlled environment of clinical research becomes a challenge, and the Food and Drug Administration set of priority recommendations for patient safety while maintaining study integrity. Fast adaptations are necessary, and actions coalesce to participant protection from COVID-19. We pointed out critical processes for adjustments, and we believe that our experience may help other academic health centers.

The COVID-19 pandemic is jostling established processes in academic health centers resulting in a profound reorganization of its clinical operations. The management of resources to prioritize COVID-19 patients raises concerns such as those with chronic diseases, including cancer. Cancer is a potentially life-threatening disease, and, to many patients, particularly in developing and emerging countries, participation in clinical trials represents an alternative means of treatment. The environment to conduct clinical trials requires well-controlled procedures regularly performed in in-person visits. Contrasting, social distancing, and the isolation of infected individuals have long been the primary strategy to fight infectious diseases. The complexities of the pandemics are moving the clinical research toward a high level of uncertainty, and resolute alternatives such as halting research activities are neither feasible nor desirable.

The Food and Drug Administration (FDA) published guidance to industry, investigators, and institutional review boards (IRB) on conducting clinical trials during the COVID-19 pandemic [1]. The orientations prioritize participant safety and study activities could be adapted to achieve the best possible level of patient welfare, otherwise recommending to decision-makers to discontinue study participation if risks outweigh potential benefits. Modern drug clinical trials run in multiple sites worldwide, which have been drastically affected by the COVID-19 pandemic, particularly with couriers’ logistics for sample shipping, delivery of investigational products to centers, and to import and export study materials.

Withholding or deferring recruitment temporarily during the COVID-19 pandemic could prevent potential risks of candidates to participate in studies that might end up unfinished. It may be necessary to reorganize infrastructure, reestablish logistics, and normalize lockdowns to permit in-person visits. From the participants’ perspective, unavoidable non-compliance with study schedules and procedures may be anticipated. Practical obstacles like patient consent withdrawal due to fear of COVID-19 exposure, missed appointments due to lack of transportation, and treatment-toxicity related examination constraints (i.e., shortage of ophthalmologists and otolaryngologists to evaluate immunologic treatment-associated adverse events) require adaptations (Table 1). Upon efforts on adjustments, clinical trials should be conducted at a reasonable safety level. In our institution, we interrupted recruitment of all protocols for eight weeks, and 107 days after the 1st death occurred in March 18th [2], no dropouts or discontinuation due to COVID-19 were registered. The participants continue to receive experimental treatment during contingency according to protocols, and the primary objectives were successfully assessed.

The local site workforce responsible for managing study requirements is multidisciplinary, and an expert team typically requires months of training to achieve an adequate level of experience. The new coronavirus outbreak may cause substantial staff infection and reduction, which may impact the ability to coordinate all corrective and preventive actions. Also, there is a growing possibility of research...
Guarantee of treatment availability and logistics

- Postponement of the activation of sites that have not yet been initiated until logistics normalization.
- Make 4–6 months planning for drug supply to included patients.
- Consider home delivery of medications, especially oral drugs.

Keep participant well informed and safe

- Inform the participants of all study changes and adaptations immediately.
- Confirm the availability of infrastructure supporting clinical research and related supply.
- Consider enrolment interruption temporarily if minimum safety support requirements are not met or are in potential risks.

Reduce the risk of COVID-19 exposure

- Limit in-person visits to safety check-ups and primary endpoint assessments and use telemedicine for non-complex procedures such as laboratory check-ups.
- Grouping all the labs, imaging, and drug infusions on the same day of medical visits to reduce the total number of hospital visits.
- Use the phone, and online platforms for video conferences with participants to respond to questionnaires.
- Offer transportation alternatives for home-site and site-home travels to avoid mass public transportation.

Keep the validity of data and sample collection

- Expand the use of a risk-based monitoring (RBM) approach and remote monitoring as much as possible.
- Update Case Report Forms (CRF) and informed consent to add information regarding COVID-19 infection.
- Consider COVID-19 disease as a potential confounder during analyses of results.
- Consider maintaining in-person monitoring visits with hygiene protocols in handling documents and social distancing with physical barriers among monitors and site staff. Adaptations in the infrastructure might be necessary.
- Confirmed COVID-19 cases should be tested until negative results. Tests should be reimbursed by the sponsors. Clinical trial participation interruption should be evaluated individually.
- Consider adaptive efforts in biological sample handling according to WHO COVID-19 guidelines to continue functional biobanking.

Improve principal investigator, sponsor, and IRB communication

- Maintain and improve the communication with sponsors for adaptations of protocol schedules and procedures prioritizations.
- Immediately communicate the IRB regarding any urgent adjustments for safety purposes.

Table 1
Adjustments of oncology clinical trials.

| Guarantee of treatment availability and logistics |
|--------------------------------------------------|
| • Postponement of the activation of sites that have not yet been initiated until logistics normalization. |
| • Make 4–6 months planning for drug supply to included patients. |
| • Consider home delivery of medications, especially oral drugs. |

Keep participant well informed and safe

- Inform the participants of all study changes and adaptations immediately.
- Confirm the availability of infrastructure supporting clinical research and related supply.
- Consider enrolment interruption temporarily if minimum safety support requirements are not met or are in potential risks.

Reduce the risk of COVID-19 exposure

- Limit in-person visits to safety check-ups and primary endpoint assessments and use telemedicine for non-complex procedures such as laboratory check-ups.
- Grouping all the labs, imaging, and drug infusions on the same day of medical visits to reduce the total number of hospital visits.
- Use the phone, and online platforms for video conferences with participants to respond to questionnaires.
- Offer transportation alternatives for home-site and site-home travels to avoid mass public transportation.

Keep the validity of data and sample collection

- Expand the use of a risk-based monitoring (RBM) approach and remote monitoring as much as possible.
- Update Case Report Forms (CRF) and informed consent to add information regarding COVID-19 infection.
- Consider COVID-19 disease as a potential confounder during analyses of results.
- Consider maintaining in-person monitoring visits with hygiene protocols in handling documents and social distancing with physical barriers among monitors and site staff. Adaptations in the infrastructure might be necessary.
- Confirmed COVID-19 cases should be tested until negative results. Tests should be reimbursed by the sponsors. Clinical trial participation interruption should be evaluated individually.
- Consider adaptive efforts in biological sample handling according to WHO COVID-19 guidelines to continue functional biobanking.

Improve principal investigator, sponsor, and IRB communication

- Maintain and improve the communication with sponsors for adaptations of protocol schedules and procedures prioritizations.
- Immediately communicate the IRB regarding any urgent adjustments for safety purposes.

The decision-making to recruit and maintain the participant in oncology clinical trials is stressful as the pandemic influences the reasonability of balancing the risks and benefits. Sharing decisions with sponsors and IRBs would be necessary for choosing the best possible compromise of participants’ safety while maintaining data quality. As COVID-19 continues to spread, the pandemics’ duration and severity will dictate further difficulties requiring immediate adaptations that may eventually be permanent. Quarantines and lockdowns programs are used to control disease propagation, but participants might be infected. A dedicated COVID-19 pavilion and operators for confirmed cases can maintain virus-free areas for cancer patients. Still, personalized patient-centered care in clinical research will change toward community care where the pandemic solutions are necessary for the entire population. Participants’ safety is paramount and efforts to prevent contamination should be the primary objective while fast operational adjustments contribute to the study integrity.
References

[1] U.S. Food and Drug Administration, FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency, Guid Doc, 2020, pp. 1–29 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency.

[2] World Health Organization, World health organization dash board, 2020. https://covid19.who.int/region/amro/country/br.

[3] A. Mehrotra, K. Ray, D.M. Brockmeyer, M.L. Barnett, J.A. Bender, Rapidly converting to ‘virtual practices’: outpatient care in the era of Covid-19, NEJM Catal (2020), https://doi.org/10.1056/CAT.20-0091.

[4] L.Y.W. Lee, J.B. Cazier, T. Starkey, C.D. Turnbull, R. Kerr, G. Middleton, COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study, Lancet 395 (10241) (2020) 1919–1926, https://doi.org/10.1016/S0140-6736(20)31773-9.

[5] World Health Organization, Criteria for releasing COVID-19 patients from isolation, 2020. https://www.who.int/news-room/commentaries/detail/criteria-for-releasing-covid-19-patients-from-isolation. (Accessed 7 July 2020).

[6] R.P. Riechelmann, R. D’Alpino Peixoto, G. Dos Santos Fernandes, et al., Evidence-based recommendations for gastrointestinal cancers during the COVID-19 pandemic by the Brazilian Gastrointestinal Tumours Group, Eecancermedicalscience 14 (2020) 1–16, https://doi.org/10.3332/ecancer.2020.1048.

[7] R.J. Arai, E.S. Longo, M.H. Sponton, M.D.P.E. Diz, Bringing a humanistic approach to cancer clinical trials, Eecancermedicalscience 11 (2017), https://doi.org/10.3332/ecancer.2017.738.

[8] R.J. Arai, R.S.C. Guindalini, A.S. Llera, et al., Personalizing precision oncology clinical trials in Latin America: an expert panel on challenges and opportunities, Oncol. 24 (8) (2019), https://doi.org/10.1634/theoncologist.2018-0518.

[9] World Health Organization, Laboratory biosafety guidance related to coronavirus disease (COVID-19), Interim Guid (19 March) (2020) 1–5, https://doi.org/10.1016/j.jcm.2016.11.007.

[10] Centre TD and C, How is COVID-19 affecting UK biobanking?, 2020. https://biobankinguk.org/how-is-covid-19-affecting-uk-biobanking/. (Accessed 7 July 2020).