**Title: Life after COVID for cancer clinical trials**

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The authors have no conflicts of interest to declare.

The PACE-C study is supported by The Royal Marsden Cancer Charity and Accuray Inc. PRIMETIME and PIVOTALboost are supported by Cancer Research UK.

**Life after COVID for cancer clinical trials**

COVID has had a huge impact on clinical research, including ongoing clinical trials of radiation therapy. Whilst we don't know what course the pandemic will take, cancer will continue to be diagnosed. It is therefore imperative that we pursue our efforts to improve cancer treatments through randomised trials and other well conducted research. Here, I reflect on the mitigations put in place in the UK and at our clinical trials unit (CTU) during the pandemic and how they may change the future clinical trials landscape.

*Trial governance*

During the pandemic, processes were defined for rapid review of COVID research by ethics and regulatory committees. This may not be scalable across a wider portfolio of clinical research in the long-term but, whilst protecting the scientific, clinical and ethical integrity of cancer research, we must seize the opportunity to retain some pragmatism and reduce the bureaucracy associated with the set-up and regulatory governance of clinical trials. The use of digital signatures that satisfy audit and regulatory requirements would seem a "quick-win" in reducing the paper trail that burdens many areas of clinical trial research administration.

*Capacity for clinical trials*

Within many healthcare systems, priority for research has been given to COVID related initiatives leading to near zero capacity to support other clinical trials. In the UK, many sites temporarily paused recruitment of patients into cancer trials and set-up of new studies. Where it was safe to do so sponsors kept trials open. This allowed patients already enrolled to continue with treatment and, recognising that in multi-centre studies the pandemic would peak in different areas at different times, provided access to clinical trials should the local investigator feel this was appropriate. Exceptions were largely where eligibility or safety monitoring required real-time analysis of patient samples at a central research laboratory which was temporarily closed to comply with Government "lockdown" conditions. As clinical trial activity resumes the continued viability of individual trials has been assessed by sponsors and independent oversight committees. Reliance on a single laboratory is a potential "pinch-point" for re-start and, where the science allows, should perhaps be avoided in the future.

*Risk reduction for trial participants*

A number of risk reduction strategies have been widely implemented and have potential to lead to longer term efficiencies in trial conduct. Telemedicine and approaches to remote consultation rolled out as part of standard care during the pandemic may well endure. Many trials already permit telephone follow up and this is likely to increase. Where they are not required for safety, arbitrarily tight or unnecessary timelines on eligibility assessments could be removed or relaxed or local standards accepted. This may improve generalisability of clinical trial results. In the future we could see more permissive eligibility criteria in phase III confirmatory trials, flexibility around where assessments are performed and triggered visits to the cancer centre for patients experiencing side effects or symptoms of relapse rather than visits mandated for all trial participants.

Historically informed consent has typically involved face-to-face discussions between the clinical team and the patient. These discussions could involve multiple team members at different timepoints and whilst they usually coincide with visits for clinical assessments this is not always the case. Where protocols do not mandate face-to-face consultation, we have therefore supported sites moving to remote consent procedures, providing they are adequately documented. If site staff and patients are comfortable with this approach it will remain as an option post COVID. Fully functional e-consent processes will no doubt become more widespread in the future. Whether remote consent and remote follow-up approaches impact on recruitment or retention of trial participants remains to be seen.

The risk:benefit ratio of all aspects of treatment needs to be carefully considered whilst COVID is pandemic in hospitals and the community. This appraisal of each assessment should be carried over into future clinical trials. Greater distinction between the necessary and the "nice to have", balancing what is key to ensure patient safety and answer the research question against the opportunity to address secondary research hypotheses, could reduce burden on patients and participating sites alike making trials sleeker and easier to deliver

*Data capture*

In the UK, like in many parts of the world, the pandemic led to home working "en-masse" and CTUs were no exception. At ICR-CTSU our established use of electronic remote data capture (eRDC) enabled data collection to continue and there was minimal impact on the ongoing oversight, review and central monitoring of data with CTU staff able to remotely and securely review and query data entered by participating sites. The pandemic has accelerated our phasing out of older technologies (e.g. use of fax) and forced rapid adaption of other systems that previously required office based working.

At the height of the pandemic, other priorities at sites and the move to home working saw a reduction in data submissions. Where trial visits or assessments were missed or delayed due to COVID, consistent recording will assist with the interpretability of trial data. The UK clinical trials community are engaging with NHS Digital so that COVID related data for clinical trial patients can be captured through routine datasets. Greater sharing of data and a paradigm shift in access to data routinely submitted to national datasets could revolutionise data collection in clinical trials. We must capitalise on the rapid progress that COVID research has driven in this area.

The collection of patient reported outcomes (PROs), often key in trials of radiotherapy, has perhaps been more impacted by COVID than physician assessed toxicity assessments. In our trials paper questionnaires are typically given out in clinic or mailed to the patient's home address directly by CTU staff and in many cases this has paused during home working. The use of electronic PROs in academic multi-centre clinical trials is increasing but implementation requires careful thought and many envisage that a mixed methods approach will be preferable to minimise participation bias. The increase in digital literacy and the drive for app-based COVID symptom reporting and alert tools is however an opportunity to revolutionise how we interact with and collect data from trial participants.

*Data analysis*

The impact of COVID on the analysis of clinical trials will depend to some extent on the stage of the trial during the pandemic. The risk of COVID-19 infection, comorbidities and mortality will need to be accounted for, or factored-in. Advanced cancer trials with death as a primary endpoint where data were maturing around the time of the pandemic may need to account for competing risks. Trials in good prognosis early disease with progression endpoints where recruitment was just taking off and events are not expected to accrue for several years will be less impacted. The impact of missing data, including PROs, will also need to be carefully assessed on a trial by trial basis.

*Case studies*

Trials testing radiotherapy hypofractionation or treatment de-escalation are anticipated to be amongst the first to re-start widely. PACE-C (NCT01584258; testing 5 fraction prostate radiotherapy in high risk patients) continued to recruit throughout the height of the pandemic albeit with recruitment in April and May 2020 at 17% of pre-COVID levels. Enthusiasm for the trial remains high given the reduction in patient visits with accrual in June already at pre-COVID levels. The protocol has been amended to temporarily relax entry criteria relating to the duration of hormone therapy permitted prior to radiotherapy, reflecting the change in clinical management during COVID. This will mean that a cohort of patients will still have the opportunity to join the trial, albeit later than they might have otherwise done. Hormone therapy duration will be accounted for in statistical analyses.

PRIMETIME (ISRCTN41579286) is a single arm study evaluating omission of radiotherapy in very low risk breast cancer patients. Risk scoring requires central testing of Ki67 performed at one of three central laboratories. One laboratory temporarily closed due to COVID and the other two had reduced capacity therefore new registrations to the study for Ki67 testing were halted. Samples already received were shipped to the two open laboratories for processing and recruitment into the main trial during April and May was maintained at 28% of pre-COVID levels. The study has now fully re-opened.

The re-start of more complex radiotherapy trials is likely to be slower. PIVOTALboost (ISRCTN80146950; testing prostate + pelvic node radiotherapy with or without an imaging defined tumour boost) was recruiting at a rate of 34 patients per month prior to the pandemic and had reached approximately 40% of its accrual target. In April and May 2020 recruitment fell to 4% of pre-COVID levels. Many UK departments are now re-starting prostate radiotherapy but estimates suggest it may take up to 6 months for recruitment rates to achieve pre-pandemic levels as the increased complexity of planning and treatment delivery required for the trial may limit a site's capacity whilst the back-log of patients awaiting treatment are seen. Co-incidentally a recent protocol amendment had permitted the use of cone beam CT for image-guidance as an alternative to fiducial markers. We anticipate that this option will accelerate re-start activities in sites where surgical capacity for insertion of fiducials remains limited. Whilst the recruitment period may be a little longer than planned the extended follow-up period of patients recruited prior to the pandemic may offset timelines for analysis which is event driven.

*Summary*

The COVID pandemic has raised the profile of clinical research and randomised trials amongst the general public. This could be an opportunity for wider engagement and participation in cancer clinical trials. As a community we need to make our clinical trials more efficient: accelerating the time from study concept to changing practice, building on routine clinical practices and utilising routinely collected data where appropriate to reduce research waste. Now more than ever we must strive to design and deliver efficient clinical trials that answer key questions that have the potential to improve the lives of cancer patients.

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