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Resilience and ongoing quality care for cancer clinical trials during COVID-19: Experience from a tertiary hospital in Australia

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Abstract

Background: The COVID-19 pandemic has forced rapid system-wide changes to be implemented within cancer care at an alarming pace. Clinical trials are a key element of comprehensive cancer care. Ensuring the continuing safe conduct of cancer clinical trials in the context of a pandemic is challenging.

Methods: We aimed to describe the COVID-19 pandemic response of a Cancer Care Clinical Research Unit (CRU) of a tertiary hospital in Queensland, Australia. We used a mixed methods approach for this case study. Emailed directives from CRU managers to all CRU staff sharing were qualitatively analysed and mapped against our unit activities over longitudinal time points. Data from patient recruitment and protocol deviations were analysed using descriptive statistics.

Results: Mapping activity from 11 March to 30 September 2020 revealed rapid change during the first 2 weeks. Four key strategies to accommodate change were identified: supporting patients and families, introduction of telehealth, accessing investigational product, and social distancing. Early in the pandemic we recognised that our core key stakeholders were integral to our response. When compared to the previous 12 months, our recruitment numbers dropped markedly in early phases of the response but recovered over time, as we accommodated internal and external impacts.

Conclusion: Our experience of agility as a necessity, adapting to support patients, and managing both clinical research activity and sponsors during the height of the pandemic response is presented here in order to inform future disaster response planning by clinical trial organisations.

1 | INTRODUCTION

SARS-CoV-2, a novel coronavirus which causes the disease known as COVID-19, was identified in the Wuhan providence of China in December 2019.[1] A pandemic was declared by the World Health Organisation (WHO) on 11 March 2020. Australia's COVID-19 incidence curve began to rise sharply and alarmingly during the second week of March 2020, at which time government bodies across the country mobilised, to prepare for the crisis that was predicted to potentially overwhelm our health systems.[2] Cancer clinical research units and triallists around the world were forced to address aspects of trial conduct affected by the pandemic. Aspects included trial participant review visits, efficacy assessment, supply chain integrity for investigational product (IP), and contract research organisation (CRO) oversight, in order to preserve

clinical trial integrity where possible.[3–5] In April 2020, the US Food and Drug Administration released pandemic guidance on conduct of clinical trials prioritising participant safety and encouraged communication between various stakeholders with an emphasis on maintaining protocol consistency and clear documentation.[6] Here, we describe our CRU response to the COVID-19 pandemic as a case study, to capture the real-time adaptations made to achieve outcomes consistent with these guidelines.

2 | METHODS

2.1 | Study design

We used a mixed methods approach[7] to describe the events of COVID-19 and subsequent response by our Cancer Care Services' Clinical Research Unit (CCS CRU) between 11 March and 30 September 2020. Retrospective data sets were accessed for historical reference to compare and complement our findings.[8]

2.2 | Study site

The study site was the Royal Brisbane and Women's Hospital (RBWH), a major referral centre and tertiary teaching hospital in South East Queensland, Australia. The RBWH is situated in Brisbane but also services patients across the state and from neighbouring New South Wales. The CCS CRU consists of three clinical trials groups: medical oncology, radiation oncology, and haematology and bone marrow transplant (BMT). There are a total of 30 (full or part-time) staff which consists of clinical trial coordinators, administrative staff, and a manager for each of the three groups. The CCS CRU is co-located on campus with both inpatient and outpatient cancer services and implements a model that embeds clinical research into day-to-day care provision.

2.3 | Mixed methods approach

We used three sets of data to describe the impact and response to the pandemic including (i) emailed directives from CCS CRU managers providing COVID-19-specific updates to CCS CRU staff, (ii) data reports of patient recruitment, and (iii) study commencement and study close-out data from our clinical research unit database. The time period of quantitative datasets was from January 2019 until September 2020. Qualitative data from above email directives were collated to map the response[9] from 11 March 2020 until 30 September 2020.

2.3.1 | Review of correspondence within the CCS CRU for qualitative analysis

Correspondence was also independently coded by three investigators (AI, TP, and NR) and then organised into themes using qualitative methods.[10] Investigator AI is a senior clinical trial coordinator in medical oncology malignancies with 10 years of trials experience, TP is a senior clinical trial coordinator in haematology malignancies with 10 years of trials experience, and NR is a clinician researcher with 10 years of clinical trials experience. The final analysis was conducted by AI, TP, and NR and cross checked.

2.3.2 | Audit of the clinical research unit databases

Historical monthly recruitment rates for matched time periods from January 2018 to September 2019 were extracted from local databases. Studies closed, suspended, and continuing were extracted from the time period of 12–26 March 2020 to capture the first 2 weeks of the pandemic response. Descriptive statistics were used for results.

3 | RESULTS

On 12 March 2020, the CCS CRU was managing 202 studies, with 2099 patients in varying stages of treatment and follow-up. In line with the CCS CRU planned response, studies were individually assessed by the CCS Executive, CCS CRU staff, principal investigators, and sponsors to identify those to be suspended or continued. These data are presented in Table 1. The mechanisms of these final decisions were determined by CCS CRU and CCS Executive but sponsors also made decisions based on the COVID-19 pandemic impact globally.

3.1 | Mapping the pandemic response: The first 2 weeks

In Queensland, the initial pandemic response commenced on 12 March 2020. The qualitative mapping identified the initial very rapid pandemic response in the first 2 weeks. The timeline of events are presented in Figure 1.

3.2 | Key stakeholders in the response

The response to COVID-19 required engagement with key stakeholders. Four key stakeholder groups were identified (Figure 2). Furthermore, relevant regulatory bodies and other stakeholders in the clinical trials community (comprising groups such as CROs) were also identified through existing relationships for each individual trial. Health service stakeholders included pharmacy, diagnostic imaging, pathology services, information technology (IT) support services, and health administration. Local stakeholders included patients and their families/carers, our clinical research staff, principal investigators for individual studies, managers, and clinicians.

All sponsors provided their individual COVID-19 response processes for patient management and monitoring. These were in turn

TABLE 1 Study activity during the period of 12–26 March 2020

	Paused by CCS CRU (*n*)	Closed by sponsor (*n*)	Continued (*n*)	Total studies (*n*)
Number of studies	8	8	186	202
Comments	Two of these included delays to site initiation visits		Eight patients discontinued study participation early due to COVID-19	

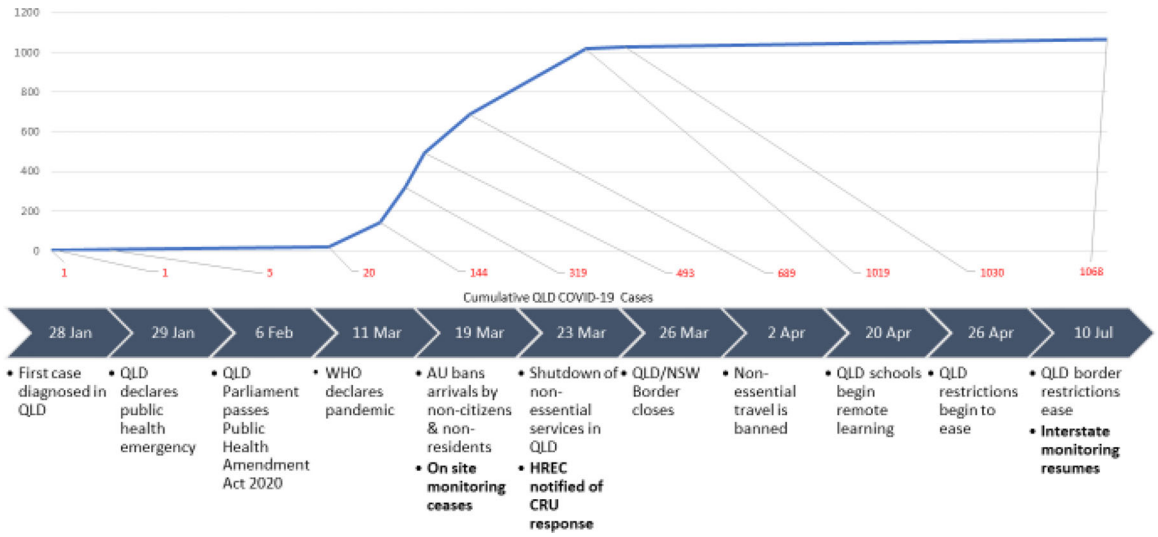

FIGURE 1 Mapping of QLD COVID-19 cases, Queensland COVID-19 events, and CCS CRU response [Colour figure can be viewed at wileyonlinelibrary.com]

submitted to the Human Research Ethics Committee office (HREC) and local research governance office (RGO).

3.3 | Strategies emergent to the response

A thematic analysis of the above-stated emailed correspondence identified four key areas where decisions and changes were systematically targeted.

The CCS Executive had quickly developed a formal response strategy across the service line, with specific directives for the CCS CRU. Regular meetings between CCS CRU managers, principal investigators/researchers, and executive were held to discuss and plan an actionable approach.

A three-phase pandemic response plan was drafted by the CCS CRU managers, with input sought by executive leadership to determine a structured decision-making framework for trial recruitment, thereby facilitating trial continuity where safe and feasible (Table 2). This three-phase plan together with notification of study suspensions were sent to the HREC and RGO. Variations to the plan included the suspension of any radiation oncology studies which collected bodily fluids such as saliva. The haematology and BMT group did not formally

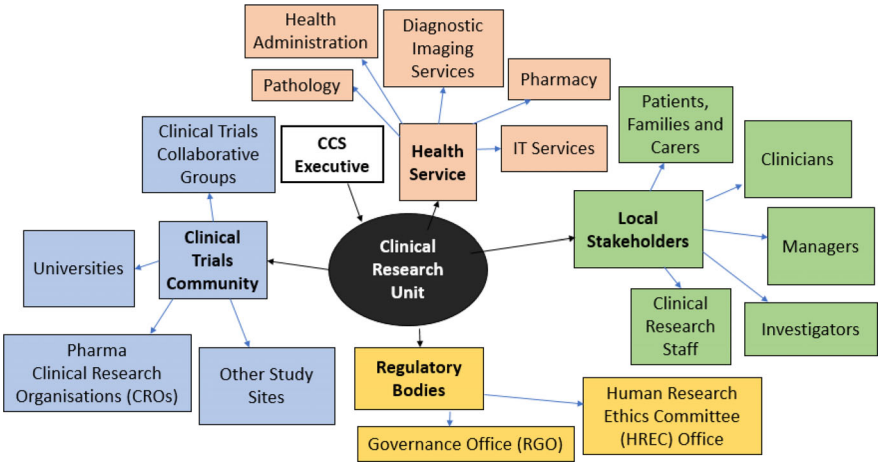

FIGURE 2 Key stakeholders engaged for the clinical research unit response to the COVID-19 pandemic [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Clinical trials pandemic response

1. Phase 1 of the response (limited COVID-19 spread):
   a. All Phase I studies immediately suspend recruitment for any patients who had not been screened or received a consent form.
2. Phase 2 of the response (widespread community COVID-19 spread apparent; healthcare provision not overwhelmed):
   a. Studies that were dependent on surgery to suspend recruitment or put on hold
   b. Cease recruitment to all observational, registry, non-interventional studies
   c. All remaining trials to continue recruitment only for patients in the local metropolitan area, and/or within the Hospital and Health Service catchment area
3. Phase 3 of the response (widespread community COVID-19 spread apparent; healthcare provision exceeded):
   a. Studies would remain open if:
      - They had curative intent
      - Used oral therapies
      - Were standard therapy with minimal additional study interventions
      - Offered unique access to treatments otherwise not available, and deemed beneficial
      - There were no other treatment options available
   b. All other studies to suspend recruitment

suspend recruitment to any study, instead focused recruitment on patients with acute disease who would most benefit from participation in a clinical trial.

Phase one of the response was implemented immediately, with the second phase projected to start within 2 weeks.

This plan also comprised of (i) the identification of participants who should attend *in-person* trial-related activities, (ii) those who could have trial protocol-mandated visits conducted *remotely* (e.g. by telehealth), or (iii) those who could cease trial-related activities *temporarily* or *permanently*.

All decisions were communicated to trial participants proactively so that patients could assess the impact and appropriate supports could be established. After the initial drafting of this plan, CCS Executive, CCS CRU managers, and principal Investigators/researchers met regularly to decide on how to respond to the most recent changing landscape of the pandemic.

3.3.1 | Supporting patients and families

As soon as the WHO declared the pandemic, patients started contacting clinical research staff to discuss their treatment plans, with approximately 20 additional queries per day. A practical plan for patients who declined to attend the site in-person due to the fear of COVID-19 infection was needed as a priority.

Standardised support and information resource tools were developed within a week to address patients' self-identified existential concerns. Many patients expressed that the pandemic would impact their treatment or that COVID-19 was a perceived threat to their survival. Every patient study visit included a discussion that balanced the risk from COVID-19 and the benefits of treatment.

Spreadsheets of predicted patient study visit schedules were saved on a shared drive between CRU teams. Shared calendars were useful for co-ordinating patient care when large numbers of staff were not available due to unscheduled leave for mandatory COVID-19 testing and quarantine.

A COVID-19 symptom screening tool was developed in line with CCS policy. Site study coordinators would contact patients by telephone a day before their scheduled study visit for COVID-19 screening. If any concerning symptoms were identified on the checklist, patients were instructed to call their general practitioner or attend the designated COVID-19 fever clinic. Whilst patients awaited COVID-19 testing results, ongoing support and contingency plans would continue from the CCS CRU.

3.3.2 | Introduction of telehealth

Videoconference was also approved as an alternative at the same time as telephone, but much more difficult to implement in practice quickly. Telephone telehealth consultations were introduced within 2 weeks for all outpatients' clinics across the hospital. Telehealth by telephone was also transitioned into care for all study visit assessments so patients could be isolated at home. This started immediately for patients on oral therapies and for follow-up visits after study treatments completion.

Prior to the pandemic, clinical trial telehealth had not been possible for two key reasons: it did not meet protocol-specific assessments mandated to be conducted on site, and it was not endorsed by Medicare or Queensland Health. COVID-19 risk triggered early discussions with sponsors so that protocol-specified assessments continued whilst keeping patients safe. Concurrently, CROs were evaluating their protocols and planned study timelines/outcomes, enabling ongoing access to study treatment for patients.

Logs were developed to track protocol deviations for CRO and HREC reporting. The newly developed protocol deviation logs were also used to identify adaptive mechanisms to conduct study assessments (e.g. height and weight measures).

3.3.3 | Accessing IP

CRU staff, the clinical trial pharmacy, and study sponsors discussed a plan for IP delivery to trial participants who were isolated at home with access to telehealth, or who were only attending trial site on a limited basis. Couriers were assessed and engaged accordingly to

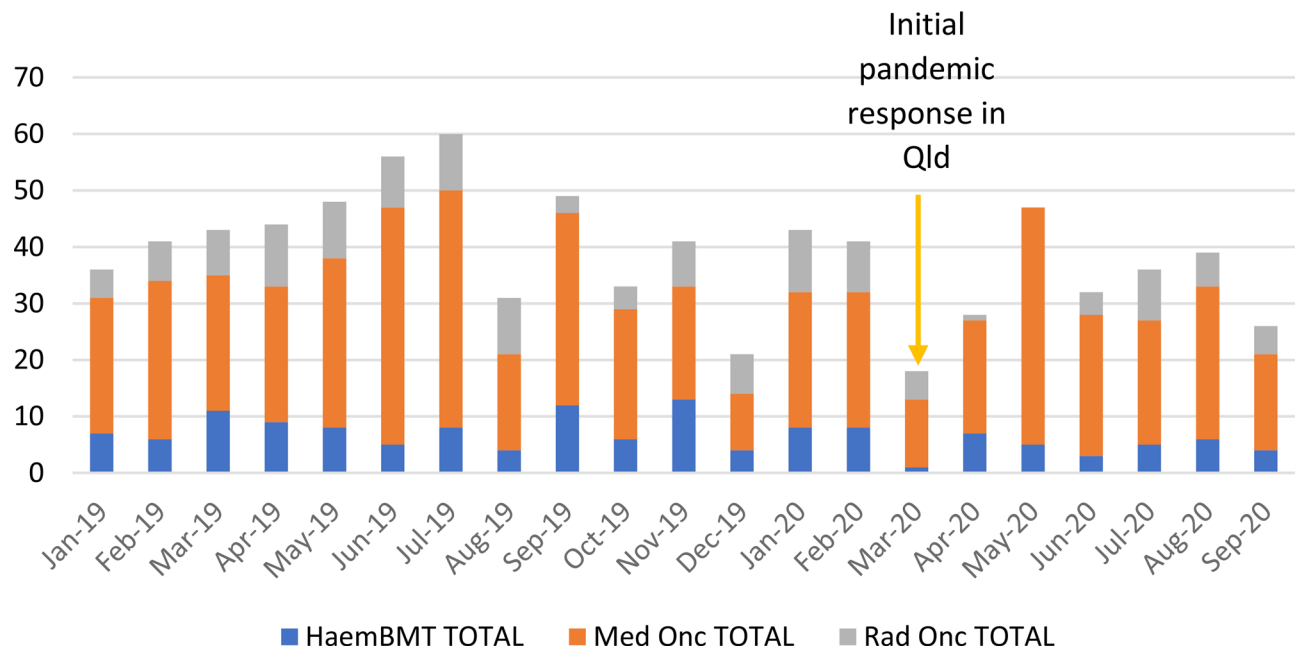

FIGURE 3 Patients consented per month [Colour figure can be viewed at wileyonlinelibrary.com]

ensure IP could be shipped safely so that it was closer to patients' homes. Standardised Operating Procedures (SOPs) were written specific to IP returned by patients that may have been contaminated with COVID-19.

3.3.4 | Social distancing

Staff were required to work under social distancing guidelines as per health service directives and workspaces were individually assessed. The area designated for clinical trial monitors was reallocated, allowing additional room for CRU staff to limit crowding in shared offices. Dividing barriers were constructed between desks.

Uptake of virtual meetings was initially challenging due to a lack of equipment, such as webcams or headsets. Staff struggled with the different virtual meeting platforms but adjusted with time. Eventually all meetings became virtual because usual meeting rooms did not allow sufficient space to meet social distancing requirements, and larger rooms were over-subscribed.

3.4 | Clinical trials unit activity during the COVID-19 response

Monthly data for patient recruitment were assessed (Figure 3). Recruitment to clinical trials in March 2020 decreased by 54.8% when compared to March 2019. Patient recruitment numbers during April 2020 began to recover; 31 patients were enrolled compared to 35 in April 2019, and 19 in March 2020.

3.5 | Responding to change: Beyond week 2 of the pandemic

3.5.1 | The external factors

By April 2020, there were increasing concerns about lack of sufficient Personal Protective Equipment (PPE) across the facility which was rationed accordingly. Patients raised concerns about the lack of visible PPE.

When Australia closed its international borders, travel restrictions impacted CCS CRU stakeholders, and in turn, study conduct. Border closures at a state level followed, with tiers of restrictions from the Queensland Chief Medical Officer. This added complex layers to the response coordinated by the CCS CRU teams and the day-to-day business of clinical research through border closures. For example RBWH services some interstate patients especially northern NSW; therefore, COVID-19 testing, permits, and travel provisions were meticulously arranged for such patients to be able to continue study treatments.

The CCS CRU trial assessment area in oncology outpatients was re-designated to accommodate a clinic screening area specifically for unwell oncology outpatients. Dedicated COVID-19 wards were set up within the hospital.

Local Clinical Research Assistants (CRAs) were in short supply and thus began to take on on-site responsibility for studies for their interstate colleagues. This placed further demands on CRU staff to support those CRAs who were unfamiliar with new studies, particularly when the Queensland borders were closed. During the tiers of response, CRAs were classified as non-essential visitors to the hospital, and as a result were not allowed on site in line with restrictions. Therefore,

monitoring ceased during this period as an alternative could not be established.

3.5.2 | Returning to the 'new normal of business as usual'

Over time, it became apparent that the feared COVID-19 infection rates had not occurred as predicted. In May 2020, the CCS CRU began to welcome Queensland-based CRAs back to site in-person under a new set of processes developed to accommodate COVID-19 restrictions. This was a new challenge as there were no shared guidelines between the contracted CRAs, HRECs, and RGO.

With a new monitoring space already in place, a more formal process was developed with strict time slots for monitoring. CCS CRU staff could no longer sit together with CRAs in the same desk space to answer queries. Instead larger rooms (which were in short supply) had to be booked to hold discussions or Microsoft Teams was used as an alternative.

CRAs had to complete a screening checklist to confirm travel, contacts, and symptoms prior to attending site. CCS CRU staff shared information about federal, state, and local guidance to ensure requirements remained current and responsive to the contemporary nature of national and international conduct of clinical trials.

Recruitment holds instituted at site were fully lifted in May, and by June all studies were open and operating except for one. In late June, Queensland announced a roadmap to reopen its state borders, although international borders remained closed. Flights began to increase again, making it easier for regional patients to attend the study site.

3.5.3 | Responding to the second wave of COVID-19 infection rates

On 30 June 2020, a second wave of COVID-19 cases in Melbourne occurred. There was also increasing concern for community transmission in Brisbane, which triggered another lockdown. Tiers of response from our hospital health service fluctuated dynamically to manage the impact of infection rates emerging in the local community. The CCS CRU guidelines from the early rapid response to the pandemic were re-evaluated and re-instituted.

Most importantly, the first wave preparation phase had helped us to now quickly identify key stakeholders and their needs, and how to most effectively share information effectively.

4 | DISCUSSION

The rapid movement of change during the COVID-19 pandemic has been widely published.[11] The mapping of CCS CRU data also illuminates a rapid rate of response during initial preparations of the pandemic response. The phenomenal pace of change in 2 weeks would have normally taken at least a year. Scientific literature has now made recommendations for the triage of cancer treatment, albeit at a later stage of the pandemic and not in real time. The decisions made in the CCS CRU to manage the tiers of response were consistent with these recommendations.[2,12–14]

United interdisciplinary teams such as investigators, CCS CRU staff, clinicians, and health administrators were a success, and this is discussed in the wider literature as having a greater importance during COVID-19.[12–13] Such success is likely due to the established relationships and trust built over time. Interestingly, Nabhan et al.[3] identify that one of the major changes during this period has been the way sponsors and CROs have dealt with the reduction in frequency of monitoring and the changes to patient's visits, and have led to a more practical approach. Importantly, this has not appeared to be a major restriction to patient recruitment. Sponsors or CROs were either monitoring less frequently or to a reduced percentage of data.[3]

The impact of local health teams needing to respond quickly to external decisions has also been widely reported in the literature.[11] Patient recruitment was affected during the height of the pandemic response in March 2020. Beyond that, recruitment rates increased again showcasing our ability to adjust and minimise the impact to studies. Studies that continued beyond this time were assessed on an individual basis with stakeholder consultation. Trial participants were very anxious they would not be able to access treatment and similar concerns from the broader oncology patient population are also reported in the international literature.[13]

The use of multiple datasets makes the findings of this case study robust to inform our response to the pandemic and compare with previous benchmarks. However, this study is limited in that it is a single-site case study of one cancer care clinical research unit within a major referral tertiary teaching hospital. In addition, this work in response to the pandemic took place in the unique context of relatively low infection rates from COVID-19 and rapid pandemic recovery in our local area. Despite this, however, we developed a strategic response which could be implemented if widespread community transmission had occurred, whilst continuing to function in the face of stringent restrictions.

Importantly, the COVID-19 pandemic has provided the opportunity to consider lasting adaptations and changes which can be incorporated into routine practice. For example the Australian healthcare system has embraced the use of new IT solutions, including telehealth, more swiftly than it would have otherwise. This is of particular relevance in locations such as ours which are characterised by vast geographical areas with low population density. Studying the adaptations in cancer care during the pandemic also provides an opportunity to assess innovations[12] and clinical trials units should be at the vanguard of this. Future clinical trial designs could incorporate opportunities for telemedicine ('Teletrials') where practical to reshape participant safety assessments and allow off-site assessments as part of the trial protocol. Such adaptations rely on the evaluation of the use of telehealth to inform future research.[12] For the CCS CRU, telehealth relied heavily on telephone consultations which had not been endorsed prior to the pandemic. The use of telephone and video conferencing for patient

consultations requires a broader knowledge base, and the impact of this on the end user could be explored in future research.

During the pandemic, sponsors have become more flexible with study procedures. As a result, research has become more patient focussed whilst ensuring safety and treatment continuity. Patients who live in regional areas have been allowed to have assessments performed with their local medical practitioner, local laboratory, or local imaging provider with the CCS CRU staff and investigator oversight. The impact of this on trial outcome evaluation and data collection will be assessed, but if feasible could provide convenient alternatives for future trial conduct.

Other pandemic adaptations which might be suitable for more widespread adoption include the use of electronic signatures for patient consent forms using telehealth consent processes. Other potential changes could include Clinical Trial Research Agreements (CTRAs) and other regulatory documents, remote monitoring of clinical trial data, and distribution of IP such as shipping oral clinical trial medications directly to patients. There is also an ongoing search for solutions to the remote monitoring when travel restrictions and border closures impact onsite visits. From our experience, the implementation of Teletrials,[15] remote monitoring, and implementation of other IT solutions such as electronic site files and medical records were key adaptations ensuring the continuing safety of trial participants during a disaster situation such as a viral pandemic.

Our final reflection of our lived experience as CRU staff is that we were confidently able to continue quality care and data collection, sustaining and meeting local and regulatory requirements, during an unprecedented crisis. Presenting our case study may give other units who are currently navigating much larger COVID-19 infection rates a reference point to assist during this challenging time. It is apparent that we are more adaptable to change than we gave ourselves credit for. In the face of an unprecedented crisis, we came together, for our patients, to provide the best possible outcomes.

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