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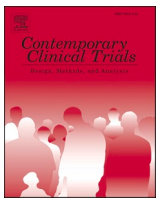

Developing resilient clinical trials: Lessons learned from rolling out the Get Back to Healthy trial during a pandemic

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ABSTRACT

Background: The COVID-19 pandemic has caused wide-spread disruptions to the conduct of randomised controlled trials (RCTs), particularly those involving public health services. Using the Get Back to Healthy trial as an example, this study aimed to contextualise the challenges imposed by the COVID-19 pandemic on implementation of RCTs involving public health services in Australia, summarise the effect of common and novel contingency strategies employed to mitigate these challenges, and describe key lessons learned.
Methods: The main challenges, the effect of contingency strategies employed, and key lessons learned were summarised descriptively.
Results: The main COVID-19-related challenge has been slow recruitment due to the suspension of clinical services for the trial target population. This challenge has been addressed through carefully considered adjustments to trial design (i.e., expanding the trial eligibility criteria), which has markedly improved trial recruitment rates. Other challenges have included the rapid transition to remote consent and data collection methods, increased complexity of monitoring participant safety, and future statistical challenges with disentangling the impact of the COVID-19 pandemic from treatment effects. The key lessons learned are: (i) adaptations to trial design may be necessary during a pandemic; (ii) offering remote methods may encourage trial participation from all age groups during a pandemic; (iii) enhanced monitoring of safety is critical during a pandemic; (iv) statistical challenges are likely to occur and should be considered when interpreting trial results.
Conclusion: Key lessons learned may be useful for informing the conduct of resilient RCTs, particularly those involving public health services, in the present and future.

1. Background

The COVID-19 pandemic has challenged the conduct of randomised controlled trials (RCTs) across the globe. In particular, RCTs relying on recruitment from public health services have been substantially affected, [1] as the rapid adoption of telehealth medicine, [2,3] cancellation or postponement of non-urgent healthcare visits, [4] and secondment of healthcare workers from non-urgent chronic care to COVID-19 and acute care services were common critical changes adopted by public health services to cope with the increasing burden of COVID-19 on global health systems. In addition, many public health services and academic institutions around the world mandated pauses

Abbreviations: LBP, low back pain; RCT, randomised controlled trial.

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on the conduct of face-to-face research activities during the pandemic, to minimise contact between trial staff and patients. [5] Many RCTs relying on recruitment and/or intervention delivery via public health services have been forced to rapidly adapt trial procedures, temporarily pause trial operations, or suspend trial activities altogether. [1].

The Get Back to Healthy trial is an ongoing pragmatic, multi-site RCT conducted in New South Wales, Australia. The trial was conceived after clinicians and consumer representatives from the outpatient physiotherapy department of partnering public hospital sites in New South Wales, Australia, identified that the lack of structured community-based support services was a strong driving factor for patients re-engaging with the health system to seek further care after discharge from treatment for chronic non-specific low back pain (LBP). To address this clinical gap, the trial was designed to investigate the effect of linking patients directly to a public health coaching program, at the point of discharge from treatment, on the future use of health services for LBP. The trial is funded by the National Health and Medical Research Council of Australia and South Western Sydney Local Health District. The involvement of public health services is criticalfor supporting recruitment as well as intervention delivery in the Get Back to Healthy trial.

Like many RCTs heavily reliant on collaborations with public health services, the Get Back to Healthy trial has faced extensive challenges with implementation during the COVID-19 pandemic. The challenges have not necessarily been unique to the Get Back to Healthy trial. For example, substantial delays with recruitment due to altered delivery of clinical services, reliance on remote consent and data collection methods, added complexity of ensuring participant safety, and potential effects of COVID-19 interfering with trial outcomes have been cited as common challenges during the pandemic. [1] Accompanying this, a collection of studies have described a range of various contingency strategies employed to overcome these challenges. However, most studies have focused on trials conducted in the United States [1,6] and United Kingdom [7,8]. To date, very few studies have reported on the specific impact of the COVID-19 pandemic on non-COVID-19 RCTs involving *public health services* in the Australian context. [9,10] Using the Get Back to Healthy trial as an example, this study aimed to provide insights into key challenges imposed by the COVID-19 pandemic on implementation of RCTs involving public health services in the Australian setting. This study also aimed to summarise the effect of common and novel contingency strategies employed to mitigate the adverse impact of these challenges on trial progress, and to describe the key lessons learned.

2. Methods

In this study, we provide an overview of the Get Back to Healthy trial. Then, we summarise the challenges imposed by the COVID-19 pandemic on the Get Back to Healthy trial. We focus on difficulties relating to slow recruitment, rapid transition to remote consent and data collection methods, maintenance of participant safety, and future statistical challenges with disentangling the impact of the COVID-19 pandemic from treatment effects. For each challenge, we describe the impact of common and novel contingency strategies employed in the Get Back to Healthy trial to minimise disruption to trial progress. To conclude, key lessons learned from implementation of the Get Back to Healthy trial during the COVID-19 pandemic are presented.

3. Results

3.1. Overview of the Get Back to Healthy trial

Detailed information on the Get Back to Healthy trial can be found in the trial protocol. [11] In summary, participants are adults recently discharged from partnering hospital outpatient physiotherapy treatment for chronic non-specific LBP. After enrolment, participants are invited to complete a baseline assessment, which involves an electronic questionnaire on demographic and anthropometric information, and health outcomes, and use of a thigh-worn accelerometer (Axivity AX3) for 7 consecutive days. At the point of discharge from treatment, participants are then randomised (1:1 allocation) either to a support system in addition to usual care ($n = 187$) or usual care alone ($n = 187$). A total of 374 participants will be recruited. Those allocated to the support system group are referred directly to a free-to-use public health coaching program called the Get Healthy Information and Coaching Service® (Get Healthy Service®). The Get Healthy Service® provides participants with up to ten telephone-based health coaching sessions, delivered by a university-qualified health coach, over 6-months. The health coaches monitor and support participants to achieve improvements in physical activity levels and personal health-related goals. The primary outcome of the trial is the total number of encounters with hospital, medical, and health services for LBP, at 12 months from baseline.

The first hospital site only received approval to commence recruitment on 23 June 2021. This coincided with the peak of the third COVID-19 wave in Australia, and corresponding introduction of public health measures. Specifically, less than one week after approval for recruitment was obtained in June 2021, a series of public health measures including lockdown restrictions, alteration of routine clinical service delivery in hospitals, and pause on face-to-face research activities, were introduced in metropolitan New South Wales, Australia. Introduction of these public health measures caused immediate disruption to trial recruitment – the first participant was not randomised into the trial until 23 December 2021 – six months after the start of recruitment. Many public health measures remained in place until November 2021; however, they were intermittently reintroduced throughout 2022. Of note, the first two waves of COVID-19 in Australia, which occurred between March to April 2020, and June to October 2020, were highly contained within specific regions (i.e., mainly affecting Victoria, Australia) and community cases were extremely low and well-controlled compared with global infection rates. Therefore, the first two COVID-19 waves in Australia were not relevant to the Get Back to Healthy trial, which was implemented in New South Wales in June 2021.

3.2. Challenges imposed by the COVID-19 pandemic on the Get Back to Healthy trial

The main challenges have been related to: (i) slow recruitment, due to suspension of clinical services for the target population; (ii) rapid transition to remote consent and data collection methods, due to government-mandated pause on face-to-face research activities at public hospitals; (iii) increased complexity of monitoring participant safety, due to short- and long-term health effects of COVID-19; and (iv) future statistical challenges with disentangling the impact of the COVID-19 pandemic from treatment effects. Slow recruitment has been the most difficult challenge to overcome.

3.2.1. Slow recruitment due to suspension of clinical services for the target population

During the COVID-19 pandemic, lower patient attendance to health services appointments has substantially impacted recruitment in clinical trials involving public health services globally. [1] In Get Back to Healthy trial, this challenge was compounded by government-mandated alteration and eventual suspension of hospital outpatient physiotherapy services for patients with chronic conditions (including chronic LBP) at most public hospitals in New South Wales, Australia. These public health measures were implemented to prioritise health service access for patients with COVID-19 as well as patients with acute conditions requiring urgent care. However, with the complete suspension of clinical services for patients with chronic LBP, the target population of the trial, this led to an immediate and complete stagnation of trial recruitment. Specifically, the first participant was only successfully recruitedinto the trial on 23 December 2021, after a small number of public hospital outpatient physiotherapy departments recommenced a limited caseload of patients

with chronic LBP.

3.2.2. Rapid transition to remote consent methods

To control the increasing rate of community COVID-19 transmission during the peak of the pandemic in New South Wales, Australia, government health agencies and academic institutions mandated a pause on face-to-face research activities. This included research conducted at public hospitals. Implementation of these public health measures immediately forced the Get Back to Healthy trial to rapidly transition to remote consent and data collection methods. Whilst the use of remote consent procedures is generally well-accepted by the research community, [7] and has become a critical tool during the COVID-19 pandemic, previous studies have reported several barriers towards implementation. Research team-related barriers include lack of relevant software to administer remote consent and reduced capacity to observe non-verbal signals to ensure participants fully understand the trial requirements before providing informed consent. [7] Participant barriers include lack of participant access to necessary technology (particularly in older adults) and participant preference for paper consent techniques due to trust and data security concerns. [7].

In the Get Back to Healthy trial, remote consent procedures were already embedded into the trial design prior to onset of the COVID-19 pandemic, [11] therefore research team-related barriers were less prominent. Necessary software to obtain remote consent were already implemented. For example, a REDCap online consent form linked with a third-party messaging service (Twilio), which allows research staff to email or text consent form links to participants, was already functional. Standard operating procedures outlining the process of conducting remote consent and ethically approved guidance scripts to assist research staff with navigation of remote consent discussions were also readily available. Research staff also received additional training to ensure valid completion of online consent forms.

Comparatively, participant-related barriers were more evident. Some potential participants, particularly older participants, were inexperienced with the use of emails or had difficulty accessing weblinks via their smartphone. Some potential participants were able to successfully access the remote consent form links without difficulty; however, they required extensive support to navigate the technical features of the REDCap online consent form. Also, a small number of potential participants cited data security concerns as a reason for declining trial participation. Nevertheless, the frequency of participant-related barriers towards remote consent appeared to reduce as the pandemic progressed. Potentially, this may have been related to increased community confidence with use of digital technologies during the pandemic [12] (e.g., teleconference health appointments, online shopping for groceries and personal items, completion of online forms for welfare payments).

3.2.3. Rapid transition to remote baseline data collection

During the COVID-19 pandemic, many clinical trials around the world were forced to rapidly transition from face-to-face to remote data collection. [1,6,7,13,14] In the Get Back to Healthy trial, participants are only offered remote methods for completion of follow-up data collection – this is a pre-existing trial feature. Participants are sent a link to the online follow-up surveys via email or text message. At the 6 month follow-up, participants are also sent an Axivity accelerometer device via post, to be worn for seven consecutive days. [11] However, for baseline data collection, both face-to-face and remote data collection methods are offered to participants. This is because, based on findings from the IMPACT pilot trial [15] which informed the design of the Get Back to Healthy trial, face-to-face completion of the baseline assessment provides research staff with greater capacity to build rapport with participants and observe non-verbal cues, and research staff can physically assist participants with ensuring accurate placement of the accelerometer device. Research staff can also provide real-time support to participants when completing the baseline survey, which is administered via an iPad during the face-to-face visit. In turn, this may build participant confidence with responding to the subsequent online follow-up surveys.

However, due to the pause on face-to-face research activities in New South Wales, Australia during the COVID-19 pandemic, the research team were forced to pivot all baseline data collection procedures to remote methods only. All participants completed the baseline assessment remotely. Several challenges were experienced during implementation. For the online survey, some participants had trouble navigating between the pages (sections) of the survey, whilst other participants had trouble re-entering the online link to continue the survey after partially completing portions of the survey. Some participants provided illogical responses to survey questions (e.g., number of days per fortnight exceeding a value of 14 days). It is likely these issues could have been mitigated via real-time support from research staff had face-to-face research visits been permitted.

For the accelerometers, extensive delays and disruptions to usual operations of the Australian national postal service resulted in the loss of several accelerometers without compensation. Due to delayed arrival of packages, challenges were also experienced in relation to depletion of accelerometer battery charge either prior to or during the seven-day period whilst the accelerometer was being worn. This specific issue resulted in data loss for several participants, necessitating the postage of replacement accelerometers so participants could repeat the assessment. Both issues have been costly for the trial, as the Axivity accelerometer costs approximately £120 per unit lost, and the cost of preparation, postage, and tracking of the replacement packages which contain the accelerometer, materials for securing the device to the participant's thigh, and a reply-paid envelope, accumulates to approximately AU$20 per additional package reposted per participant, or AU$30 per package sent via express post.

Nevertheless, despite these challenges, there have been several advantages to the use of remote baseline data collection methods during the COVID-19 pandemic. Namely, this allowed the research team to continue trial recruitment despite lockdown restrictions and recruit participants living outside metropolitan New South Wales (e.g., rural communities).

3.2.4. Challenges with enhanced monitoring of participant safety

The COVID-19 pandemic has introduced additional challenges with safety monitoring in RCTs, due to the known serious health consequences of contracting COVID-19 particularly in older populations and the long-term effects of COVID-19 which are still not fully understood. For example, to date, two participants (1%) have reported persistence of long-covid symptoms (e.g., fatigue, shortness of breath, reduced exercise tolerance) prior to enrolment and/or during trial participation trial participants. Four participants (2%) have reported contracting COVID-19 during trial participation, which temporarily prevented exercise participation. Furthermore, similar to other trials involving patients with LBP, [1] in the Get Back to Healthy trial, difficulty with access to formal care during the COVID-19 pandemic, due to social distancing measures, has resulted in exacerbation of LBP symptoms in several participants.

3.2.5. Future statistical challenges with data analysis and interpretation of trial results

The COVID-19 pandemic has introduced future statistical challenges with analysis and interpretation of trial results, due to difficulties with disentangling the physical, mental, and/or economic impacts of COVID-19 which may potentially moderate or mediate treatment effectiveness. There is also growing body of evidence demonstrating major changes in care-seeking behaviours during the pandemic. [1] This poses additional challenges for the Get Back to Healthy trial, as the primary outcome is the utilisation of hospital, medical, and health services for LBP.

3.3. Contingency strategies employed in the Get Back to Healthy trial

Pre-existing features of the Get Back to Healthy trial design have

enabled investigators to partially mitigate the magnitude of disruptions associated with some of these challenges. Nevertheless, additional contingency strategies have been necessitated to adapt to the evolving circumstances. Examples of common and novel contingency solutions implemented in the Get Back to Healthy trial and their effect on trial progress are described.

3.3.1. Strategies to address slow recruitment

During the COVID-19 pandemic, RCTs involving public health services responded differently to challenges of slow recruitment. In cases where continued trial operation was not feasible (e.g., difficulty maintaining staff and participant safety, funding limitations), trials were terminated completely, whilst others temporarily paused recruitment of new participants during COVID-19 outbreaks. [16,17] Other trials have continued with recruitment with adaptations to trial design, such as relying on external sources to support recruitment, such as charities [7]. Termination or a temporary pause on recruitment was not feasible for the Get Back to Healthy trial. Therefore, trial investigators made a pragmatic decision to rely on external sources to support recruitment. Specifically, the trial eligibility criteria and aims were adjusted to further include people seeking care for chronic non-specific LBP within the general community (e.g., from a general practitioner, physiotherapist, or chiropractor) in the last six months (Supplementary A).

The decision to expand recruitment to the general community was based on consensus amongst trial investigators and partnering clinicians that most patients with LBP seek care from community-based health care providers, especially during the COVID-19 pandemic when public hospitals suspended outpatient services for this population. Further, these patients also experience similar issues with lack of support services available after discharge from community-based care and follow similar patterns of returning to health services for further treatment. The adaptation to trial design was made after careful consideration of possible risks of introducing heterogeneity into the trial sample (e.g., potential differences in symptom presentation and/or care-seeking patterns between participants identified from public hospitals and those identified from the general community) and broadening of the original research question. Consensus was reached that the benefits of increasing recruitment rates and ensuring trial completion outweighed the possible risks, which could be addressed. The changes were approved by the reviewing ethics committee in February 2022, approximately four months after public health measures which were introduced in New South Wales in response to the third wave of COVID-19 in Australia were lifted.

The impact of expanding recruitment to the general community was immediate, with overall trial recruitment rates increasing drastically after February 2022 (Fig. 1). Of note, the recruitment rate for participants identified from public hospitals has remained low. Largely, this is because most public hospitals in New South Wales, Australia, have continued to operate on reduced caseloads of patients with chronic non-specific LBP, even at the time of report. Consequently, it can be inferred that expanding recruitment to the general community has been a key contributor towards accelerated recruitment in the Get Back to Healthy trial.

The following recruitment avenues, targeted at the general community, have been trialled: social media platforms (i.e., paid advertisements on Facebook, Google, and YouTube, free promotion of paid Facebook advertisements in community groups, unpaid posts on Twitter and Instagram); paid advertising in electronic community newsletters (Seniors Card, Your Life Choices); public health network newsletters predominantly targeted at clinicians; University websites; recruitment databases (e.g., Health Match). Table 1 summarises the cost of advertising per participant randomised for each recruitment avenue.

Overall, trends suggest that Seniors Card and YourLifeChoices, which are electronic newsletters targeted at older people, and Facebook - which are all paid advertising avenues - have been effective and cost-effective strategies for driving increased recruitment from the general community. At the time of report (20 June 2023), the most efficient and cost-effective recruitment avenue has been YourLifeChoices (AU$179 per participant randomised), followed closely by Facebook (AU$183 per participant randomised). However, with an additional 31 participants identified from Seniors Card, who are currently pending completion of the baseline assessment and subsequent randomisation, we expect that by the end of July, Seniors Card will become a more cost-effective strategy for trial recruitment (approximately AU$177 per participant randomised). In total, 195 participants have been randomised into the trial (52% of the total sample size), of which 175 (90%) have been recruited from the general community.

Fig. 1 is current as of 21 June 2023. A one-to-two-month latency between implementation of a new recruitment strategy and change in recruitment rate is considered normal in the Get Back to Healthy trial, accounting for time between trial advertising, informed consent, completion of baseline assessment, and randomisation.

However, whilst marked improvements to recruitment rates have been observed, the trial investigators acknowledge that this adaptation

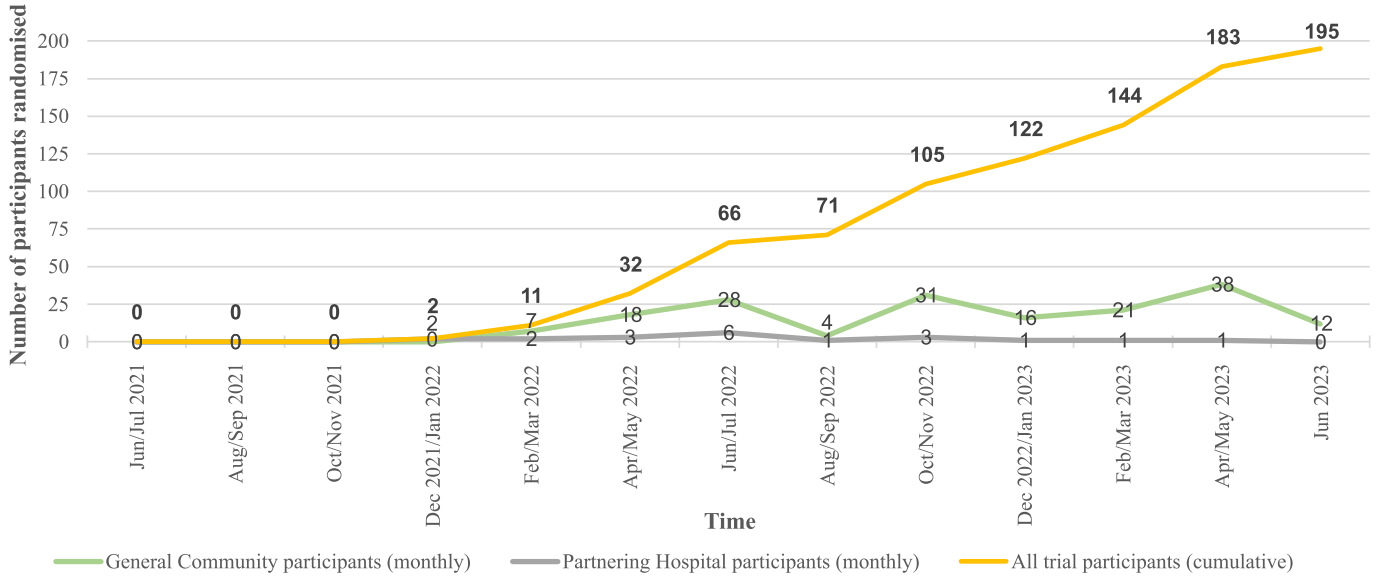

Fig. 1. Recruitment rates.

Table 1
General community recruitment sources.

Recruitment Source	Description	Timeline	Total cost (AUD)	EOI (n)	Randomised (n)	Cost/randomised participant*
Facebook	Paid advertising (boosted posts) and manual posting of advertisements in local community groups. Reach: $n = 151,238$	Mar 2022 – ongoing	$5483	140	30	$183
Google	Paid Google advertisements. Reach: Unknown	Sep 2022 – Jan 2023 (5 months)	$757	10	2	$379
YouTube	Paid YouTube advertisements. Reach: $n = 50,000$	Mar 2023 – Apr 2023 (one month)	$400	2	1	$400
Twitter	Monthly tweets. Reach: Unknown	Mar 2023 – ongoing	$0	0	0	$0
Instagram	Monthly Instagram posts. Reach: Unknown	Mar 2022 – ongoing	$0	0	0	$0
Seniors Card	Four electronic newsletter blasts. Reach: $n = 400,000$ per blast	Apr 2022, Oct 2022, Mar 2023, Jun 2023	$20,000	366	82	$244
YourLifeChoices	Four electronic newsletter blasts, co-authored blogposts, sponsored advertising on website. Reach: $n = 258,638$ per blast, 1.86 M monthly website views	Sep 2022 – ongoing	$5000	83	28	$179
Public Health Network newsletters	Electronic newsletters distributed to health districts in New South Wales, targeted at clinicians and consumers. Reach: Unknown	Feb 2023, May 2023	$0	0	0	$0
University website	Electronic dashboard of clinical trials actively recruiting participants, hosted by the University of Sydney. Reach: Unknown	Jun 2022 – ongoing	$0	3	2	$0
Health Match	Digital registry targeted at linking patients to available clinical trials. Reach: Unknown	Mar 2022 – ongoing	$0	4	1	$0
Community health services	Dissemination of advertising materials via community clinicians. Reach: Unknown	Mar 2022 – ongoing	$0	8	3	$0
Clinical trial databases	Registry of participants from previous trials interested in further research. Reach: $n = 98$	Feb 2022	$0	41	15	$0
Other sources	Participants unable to recall source. Reach: Unknown	Unknown	Unknown	54	11	Unknown

EOI: expressions of interest. All costs exclude salary costs for research staff involved in implementiion of the recruitment strategies. Costs and number of participants are current at time of report (20 June 2023).

to the trial design has altered the original research question. To address concerns of possible heterogeneity in the trial sample, exploratory analyses have been added to the statistical analysis plan to assess the potential impact of recruitment avenue (i.e., public hospitals versus general community) on treatment effectiveness. Methods of the exploratory analyses will be published in the statistical analysis plan. Qualitative interviews on facilitators and barriers to engagement in the trial intervention are also underway. Attention will be paid towards possible differences in themes emerging from those recruited from public hospitals compared with those recruited from the general community. Final trial results will be interpreted in the context of these additional findings.

3.3.2. Strategies to address challenges with remote consent

The main contingency strategies employed to address challenges related to the rapid transition to remote consent methods have been: (i) allocation of additional time for each consent call (increased from 1h to 1.5 h), and (ii) completion of the online consent form during the consent call so that research staff can provide real-time troubleshooting support for technical difficulties. [7] These strategies have provided research staff with increased capacity to build rapport with participants, confirm participant understanding of trial procedures in the absence of non-verbal cues, minimise delays in obtaining valid online consent. Teleconferencing (i.e., zoom, Microsoft teams) is also offered to participants as an option for consenting; although, most participants have preferred to perform the consent process via phone call. To address participant concerns regarding data privacy, participants are provided with reassurance of the stringent, ethically approved confidentiality protocols which are embedded into the trial design. In most cases, participants have been satisfied with the reassurance provided; however, a small number of participants have continued to decline participation.

3.3.3. Strategies to address challenges with remote data collection via surveys

The main contingency strategies employed to address challenges related to the rapid transition to remote baseline data collection, via surveys, has been the allocation of additional time during consent calls to provide participants with detailed instructions on how to navigate the survey link and features, prior to commencement of the baseline assessment. Participants are also encouraged to contact the research team immediately if they experience any confusion or difficulty with completion of the online baseline survey. Where feasible, support from research staff is provided to participants within the same calendar day. If necessary, research staff may provide real-time support over the phone whilst the participant completes the online survey. To address challenges related to illogical survey responses in the online baseline surveys, an issue which also affects the online follow-up surveys, the first contingency strategy has included the use of REDCap features to limit participant responses between logical values. For example, for questions regarding the number of days seeking care for LBP in the last fortnight, possible responses are restricted to values between zero to 14. In some instances, illogical responses are permitted by the REDCap system. To address this issue, research staff have increased the frequency of data auditing from a monthly to twice-weekly basis. Not only has this strategy allowed the research team to identify illogical responses, it has also enabled immediate identification of missing or outlier responses. A blinded research staff is then assigned to contact the participant as soon as possible to obtain or clarify the correct response. By observation, this process has substantially reduced the number of missing, illogical, and inaccurate responses in the trial data set.

3.3.4. Strategies to address challenges with remote data collection via accelerometers

Challenges related to the loss of accelerometers due to delays and disruptions to postal service activity have been difficult to address. As contingency measures, tracking stickers are placed on the packages, and the research team confirm participant availability for assessment and current postal address, prior to postage of the package. Whilst the number of lost accelerometers has reduced as the COVID-19 pandemic has progressed, it is unclear whether improvements are related to implementation of these contingency strategies or reduced delays and disruptions to the postal service. To address challenges related to the

depletion of accelerometer battery charge prior to or during the active assessment period, researchers at the University of Sydney with expertise in Axivity accelerometer devices were consulted. Suggested strategies have been trialled with noticeable success. Firstly, the start date of the recording period is delayed for ten days from the date of initialisation to account for possible delays in delivery time. Research staff also contact participants prior to their expected baseline or follow-up date, to confirm their availability to receive the package and wear the device within the following two to three weeks. Secondly, battery-draining features of the Axivity accelerometer are disabled, for example, the "flash during recording" feature is turned off. The frequency of encountering these issues has drastically reduced with a gradual return to usual postal delivery schedules in Australia combined with implementation of contingency strategies to conserve battery charge.

3.3.5. Strategies to enhance participant safety

In the Get Back to Healthy trial, several trial procedures were already embedded into the trial protocol prior to onset of the COVID-19 pandemic, such as: (i) medical clearance for participants at higher risk of adverse events, (ii) weekly adverse event monitoring, (iii) routine non-interventional follow-up calls at 3, 6, and 9 months into trial participation. [11] These procedures were enhanced during the COVID-19 pandemic to maximise participant safety. In the Get Back to Healthy trial, potential participants who self-report any comorbid health conditions which may prevent safe trial participation (e.g., uncontrolled asthma, uncontrolled hypertension) are required to obtain medical clearance from their general practitioner prior to randomisation. [11] During the COVID-19 pandemic, research staff capitalised on this trial procedure by requesting that potential participants who self-reported a recent COVID-19 infection of moderate to severe severity, or persistence of long-COVID symptoms, should also obtain medical clearance from their general practitioner. This enhanced safety procedure allowed the research team to ensure participants were medically fit to participate in the trial.

Further, all participants in the Get Back to Healthy trial are required to complete a self-reported, paper-based weekly diary. [11] The weekly diary records any adverse events which may occur during the first six months of trial participation. Participants are instructed to report the occurrence of adverse events directly to the research team as they occur. During the COVID-19 pandemic, research staff specifically reminded participants that contracting COVID-19, experiencing long-COVID symptoms, or experiencing uncontrolled flare-ups of their LBP at any point during trial participation should be reported to the research team. Upon notification, research staff then schedule follow-up calls with the participant, with the frequency determined by the severity and extent of the participant's symptoms, until symptom resolution is reported. Finally, during the routine non-interventional follow-up calls with participants which occur at 3, 6, and 9 months into trial participation, [11] research staff dedicate additional time to ascertain a participant's general wellbeing in the context of the global pandemic. If adverse events are identified during the routine follow-up call, enhanced monitoring procedures described previously are employed. Where necessary, participants are encouraged to contact their general practitioner or local social support services.

3.3.6. Strategies to address statistical challenges with analysis and interpretation

There are no simple solutions for disentangling the potential impact of the COVID-19 pandemic or related events on treatment effectiveness. Previous studies have proposed various statistical approaches, including simulations models to determine the potential impact of COVID-19 related events on the primary outcome, evaluation of temporal patterns and correlations of missing data to assess differential non-response, and investigating longitudinal trajectories in participant outcomes across treatment groups and key COVID-19 time periods. [1] Other studies have concluded that no changes to the trial protocol are unnecessary due to the likely even distribution of COVID-19 effects across treatment groups. [1]

In the Get Back to Healthy trial, trial investigators expect that the primary outcome – the utilisation of hospital, medical, and health services for LBP over one year, will likely be affected by COVID-19 events given the substantial changes to usual health service delivery for this population during the pandemic. However, the investigators also anticipate that owing to effective randomisation of trial participants across intervention groups, the effects of COVID-19 on trial outcomes will be evenly distributed across groups. Baseline characteristics of trial participants will be compared across intervention groups to determine whether effective randomisation has been achieved. To date, twice-weekly auditing of missing data has not revealed any temporal patterns in non-response in the primary or secondary trial outcomes. In addition, qualitative interviews are being conducted to ascertain possible effects of the COVID-19 pandemic on participant experience of engaging with the trial intervention. Findings will be used to guide interpretation of trial results. Furthermore, the final results of the Get Back to Healthy trial will be reported according to the CONSERVE 2021 Statement, [18] a guideline for reporting of trial protocols and completed trials which have been modified due to the COVID-19 pandemic and other extenuating circumstances.

4. Discussion

During the COVID-19 pandemic, clinical trial activity has been impacted across the globe. In particular, RCTs involving public health services have been affected substantially, due to rapid changes in usual service delivery causing disruptions to recruitment and intervention delivery and pause on face-to-face research activities warranting rapid changes to trial procedures. The Get Back to Healthy trial is an example of an ongoing pragmatic, multi-site RCT in Australia which involves public health services to support recruitment (i.e., public hospital outpatient physiotherapy departments) and intervention delivery (i.e., public health coaching program, delivered by the Get Healthy Service®). Whilst intervention delivery has not been noticeably impacted by the COVID-19 pandemic, as the trial intervention is a remote, phone-based health coaching program, the Get Back to Healthy trial has faced numerous challenges with slow recruitment, rapid transition to remote consent and baseline data collection methods, monitoring of participant safety, and future statistical challenges with disentangling the impact of the COVID-19 pandemic from treatment effects. This paper describes the effect of various common and novel contingency strategies to address the adverse impact of the COVID-19 pandemic on the Get Back to Healthy trial.

4.1. Key lessons learned

The key lessons learned from implementation of the Get Back to Healthy trial, a RCT heavily reliant on public health services for recruitment and intervention delivery during the COVID-19 pandemic have been:

1. Adaptation to trial design may be necessary during prolonged periods of slow recruitment. However, the risk-benefit ratio of potentially introducing heterogeneity into the trial sample and altering the original research question should be considered carefully, with input from end-users (e.g., consumers, clinicians).
2. Remote consent and data collection may be a feasible alternative when face-to-face research activities are not permitted or impractical to implement. During a global pandemic, remote data collection may be a useful strategy for encouraging clinical trial participation in people of all ages. [12]
3. Maintenance of participant and trial staff safety is always paramount during trial implementation. However, during a global pandemic, enhanced monitoring of safety is critical particularly when the short

and long-term impacts of pandemic-related events are not fully understood.

4. During unprecedented situations such as global pandemics, statistical challenges associated with disentangling the impact of the pandemic itself from treatment effects will likely be present. At minimum, RCTs should compare baseline characteristics of trial participants across all intervention groups to determine the effectiveness of the randomisation procedure and potential need for exploratory statistical analyses, and also report trial findings in accordance with the CONSERVE 2021 Statement. [18]

All in all, researchers may benefit from drawing upon some of the contingency strategies employed in the Get Back to Healthy trial, and lessons learned, to address COVID-19 challenges related to recruitment, data collection, participant safety, and statistical analysis. Findings may be useful for informing the conduct of resilient RCTs, particularly those involving public health services, in the present and future.

5. Conclusion

The COVID-19 pandemic has resulted in extensive disruptions to the conduct of RCTs around the world, particularly RCTs involving public health services. Using the Get Back to Healthy trial as an example, this paper contextualises the impact of the COVID-19 pandemic on RCTs relying on public health services for recruitment and intervention delivery in the Australian setting. The main COVID-19 challenges described pertain to slow recruitment, rapid transition to remote consent and data collection methods, increased complexity of monitoring participant safety, and future statistical challenges with disentangling the impact of the COVID-19 pandemic from treatment effects. Findings may be useful for informing the conduct of resilient RCTs, particularly those involving public health services, in the present and future.

Ethics approval and consent to participate

The Get Back to Healthy trial has been prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12620000889954). Ethical approval has been prospectively granted by the Western Sydney Local Health District Human Research and Ethics Committee (2020/ETH00115). Written informed consent will be obtained from all participants. Participants may choose to withdraw consent at any point during the trial duration without providing a reason. The relevant sponsor has reviewed the trial protocol and consent form.

Consent for publication

Not applicable.

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Authors' contributions

EKH drafted the original manuscript. PHF is lead investigator, and EKH is clinical trial co-ordinator of the Get Back to Healthy trial. All co-authors (EKH, MLF, PH, MH, KM, DC, MJ, ABA, MTB, PHF) contributed substantially to formal analysis, and revisions and editing of the manuscript. PHF, MLF, PH, MTB, MH, DC, ABA, MJ, EKH, and KM contributed to funding acquisition. All authors read and approved the final manuscript.

Declaration of Competing Interest

All authors have no competing interests to declare.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cct.2023.107330.

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