The impact of COVID-19 restrictions on participant enrollment in the PREPARE trial

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ABSTRACT

Background: At the initiation of the COVID-19 pandemic, restrictions forced researchers to decide whether to continue their ongoing clinical trials. The PREPARE (Pragmatic Randomized Trial Evaluating Pre-Operative Alcohol Skin Solutions in Fractured Extremities) trial is a pragmatic cluster-randomized crossover trial in patients with open and closed fractures. PREPARE was enrolling over 200 participants per month at the initiation of the pandemic. We aim to describe how the COVID-19 research restrictions affected participant enrollment.

Methods: The PREPARE protocol permitted telephone consent, however, sites were obtaining consent in-person. To continue enrollment after the initiation of the restrictions participating sites obtained ethics approval for telephone consent scripts and the waiver of a signature on the consent form. We recorded the number of sites that switched to telephone consent, paused enrollment, and the length of the pause. We used t-tests to compare the differences in monthly enrollment between July 2019 and November 2020.

Results: All 19 sites quickly implemented telephone consent. Fourteen out of nineteen (73.6%) sites paused enrollment due to COVID-19 restrictions. The median length of enrollment pause was 46.5 days (range, 7–121 days; interquartile range, 61 days). The months immediately following the implementation of restrictions had significantly lower enrollment.

Conclusion: A pragmatic design allowed sites to quickly adapt their procedures for obtaining informed consent via telephone and allowed for minimal interruptions to enrollment during the pandemic.

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1. Introduction

On March 13, 2020, the COVID-19 pandemic forced restrictions across the world to slow the spread of the novel coronavirus. In response, many hospitals and research ethics boards introduced policies limiting in-person contact, which prohibited in-person clinical research activities. For clinical trials to continue, researchers had to develop a plan for continuation that demonstrated that there is no increased risk of transmission of COVID-19 as a result of their research activities [1]. As a result, thousands of clinical trials paused or stopped participant enrollment and follow-up [2].

Pragmatic trials evaluate the effectiveness of interventions under real-life, routine conditions. One of the key benefits of pragmatic trials is that the results are more generalizable, which offers higher external validity. The PREPARE trial (Pragmatic Randomized Trial Evaluating Pre-Operative Alcohol Skin Solutions in Fractured Extremities) follows a pragmatic design. Pragmatic aspects of the PREPARE trial include cluster randomization, broad eligibility criteria, consent after surgery, use of interventions that do not require an increase in care delivery and, no additional tests, procedures, or follow-up visits. Most relevant, the PREPARE trial protocol has flexible consent (e.g. in-person and telephone) and follow-up (e.g. in-person, telephone, text, email).

In March 2020, the PREPARE trial was approximately half-way through enrollment and was enrolling over 200 participants a month. We aim to describe how COVID-19 restrictions affected participant enrollment in the PREPARE trial. Specific objectives include: 1) number of hospitals that were able to transition to a telephone consent model; 2) number of hospitals who paused enrollment; and 3) the length of the enrollment pauses and impact on overall enrollment.

2. Methods

2.1. The PREPARE trial

The PREPARE trial is a pragmatic cluster randomized crossover trial that compares iodine povacrylex (0.7% free iodine) in 74% alcohol (DuraPrep™) versus 2% chlorhexidine gluconate in 70% isopropyl alcohol (Chloraprep™) in fracture patients. Each clinical site uses the initially allocated skin preparation solution for a period of two months and subsequently crosses over to the opposite solution for their second recruitment period. This process repeats every two months for 24 months. The primary outcome is surgical site infection (SSI) as defined by the Centers for Disease Control and Prevention (CDC) [3]. The secondary outcome is unplanned fracture-related reoperations within 12 months to manage infection, wound healing problems and fracture healing problems. The PREPARE trial will enroll at least 1,540 patients with open appendicular fractures (open fracture cohort) and 6,280 patients with closed lower extremity and pelvic fractures (closed fracture cohort) at hospitals in North America. These cohorts constitute distinct patient populations with different risks of infection and data from each cohort will be analyzed separately, as described in the protocol [4]. PREPARE is registered on clinicaltrials.gov (NCT03523962) and the protocol has been published [4].

2.2. COVID-19 restrictions

Before the COVID-19 pandemic, all clinical sites obtained informed consent in person at their hospital or fracture clinic. However, after March 13, 2020, COVID-19 restrictions limited in-person consenting at most participating hospitals. Affected clinical sites were encouraged by the trial Methods Centre to transition to telephone consent, which was already included as a consent option in the PREPARE protocol. Prior to implementing telephone consent, clinical sites had to determine local logistics and obtain ethics approval for telephone consent scripts and procedures. Rapid ethics approval to waive the requirement for a participant’s written signature on the informed consent form was also obtained from the central ethics committee and local ethics committees (for sites not using the central ethics committee) was also obtained.

2.3. Statistical analysis

For clinical sites that were enrolling participants at the onset of the pandemic, we descriptively evaluated the number of clinical sites that transitioned to telephone consent, the number of clinical sites that had to pause enrollment, and the length of the enrollment pauses.

We evaluated monthly enrollment from July 2019 to November 2020. For this evaluation, we included sites that completed at least eight months of enrollment prior to the onset of the pandemic. Results are stratified by open and closed fracture cohorts and are summarized using descriptive statistics. Statistical analysis using paired t-tests were also used to compare the differences in monthly enrollment. Data analyses were conducted using R (version 4.0.0, R Foundation for Statistical Computing, Vienna, Austria).

2.4. Results

At the onset of the pandemic on March 13, 2020, 19 clinical sites were enrolling participants into the PREPARE trial (Table 1). Fourteen (73.6%) clinical sites paused enrollment due to COVID-19 restrictions, while they transitioned to telephone consent models. The median length of enrollment pause was 46.5 days (range, 7–121 days; interquartile range, 61 days). By July 15, 2020, all clinical sites resumed enrollment. Fifteen (78.9%) sites transitioned to telephone consent and four (21.1%) clinical sites continued with in-person consent.

Thirteen clinical sites had eight full months of enrollment prior to the COVID-19 pandemic. The average monthly enrollment prior to COVID-19 restrictions was 198 participants in the closed fracture cohort (standard deviation (SD) 22, range: 161–227) and 41 participants in the open fracture cohort (SD 16, range: 22–60). Enrollment was the lowest in April 2020, when 47 participants in the closed fracture cohort and nine participants in the open fracture cohort were enrolled. Enrollment began increasing in May 2020 in the open fracture cohort and in June 2020 in the closed fracture cohort - coinciding with clinical sites resuming enrollment.

From June 1, 2020, to November 30, 2020, the average monthly enrollment rates were 183 participants in the closed fracture cohort (SD 30, range: 129–206) and 44 participants in the open fracture cohort (SD 12, range: 24–61), which were close to pre-COVID enrollment numbers. Fig. 1 shows enrollment numbers during this period.

From June 1, 2020, to November 30, 2020, the average monthly enrollment rates were 183 participants in the closed fracture cohort (SD 30, range: 129–206) and 44 participants in the open fracture cohort (SD 12, range: 24–61), which were close to pre-COVID enrollment numbers.

March, April, and May 2020 had significantly lower enrollment in the closed fracture cohort (p = 0.01) and March and April 2020 had significantly lower enrollment in the open fracture cohort (p = 0.04). Enrollment was similar in all other months.

From July 1, 2019, to February 28, 2020, 798% of eligible patients approached were enrolled into the PREPARE trial. During the period of COVID-19 restrictions (March 13, 2020, to May 31, 2020) where telephone consent was primarily used, this percentage increased to 81%.

From June 1, 2020, to November 30, 2020, the percentage of eligible patients approached who were enrolled into the PREPARE trial decreased slightly to 79%.

3. Discussion

The PREPARE trial is a pragmatic high-enrolling clinical trial that was approximately half-way through enrollment at the start of the COVID-19 pandemic. Fourteen of the nineteen clinical sites in the
Enrollment pause details.

| Cluster | Location | Enrollment Pause Date | Enrollment Restart Date | Duration of Pause (Days) |
|---------|----------|-----------------------|-------------------------|--------------------------|
| Duke University | Durham, North Carolina | No Pause | No Pause | No Pause |
| Hamilton Health Sciences | Hamilton, Ontario | No Pause | No Pause | No Pause |
| Regional Medical Center of San Jose | San Jose, California | No Pause | No Pause | No Pause |
| Sanford Health | Sioux-Falls, South Dakota | No Pause | No Pause | No Pause |
| University of Utah | Salt Lake City, Utah | No Pause | No Pause | No Pause |
| R Adams Cowley Shock Trauma Center | Baltimore, Maryland | March 15, 2020 | March 22, 2020 | 7 |
| Mississippi Medical Center | Jackson, Mississippi | March 18, 2020 | April 7, 2020 | 20 |
| Dartmouth-Hitchcock Medical Center | Lebanon, New Hampshire | March 18, 2020 | April 13, 2020 | 26 |
| IU Health | Indianapolis, Indiana | March 17, 2020 | April 15, 2020 | 29 |
| Wake Forest Baptist Health | Winston-Salem, North Carolina | March 17, 2020 | April 21, 2020 | 35 |
| Penn Presbyterian Medical Center | Philadelphia, Pennsylvania | March 13, 2020 | April 23, 2020 | 41 |
| Inova Fairfax Medical Campus | Falls Church, Virginia | March 18, 2020 | May 1, 2020 | 44 |
| MetroHealth | Cleveland, Ohio | March 16, 2020 | May 4, 2020 | 49 |
| San Antonio Military Medical Center | San Antonio, Texas | March 20, 2020 | June 1, 2020 | 73 |
| Royal Columbia Hospital | New Westminster, British Columbia | March 17, 2020 | June 4, 2020 | 79 |
| Brigham and Women’s Hospital | Boston, Massachusetts | March 16, 2020 | June 16, 2020 | 92 |
| Massachusetts General Hospital | Boston, Massachusetts | March 16, 2020 | June 16, 2020 | 92 |
| University of Maryland Capital Region Health | Cheverly, Maryland | March 17, 2020 | June 15, 2020 | 90 |
| Prisma Health | Greenville, North Carolina | March 16, 2020 | July 15, 2020 | 121 |

Fig. 1. Prepare trial monthly enrollment.

PREPARE trial paused enrollment in response to the initial restrictions. Five clinical sites did not pause enrollment. Reasons for this include a quick transition to telephone consent or local policies which allowed in-person consent to continue with modifications including personal protective equipment and social distancing. Reasons for variation in the duration of the enrollment pause at clinical sites include differences in hospital policies, differences in the prevalence of COVID-19 transmission in each region, changes in research personnel, and differences in the ability of research personnel to adjust to remote work environments.

Key pragmatic features of the PREPARE trial that aided with study continuation during the initial restrictions include the lack of tests, visits, and procedures outside of usual care practices and the flexibility for remote follow-up visits. These features allowed the study to be conducted without exposing participants and study personnel to settings that would increase the risk of COVID-19 transmission. The pragmatic nature of the trial also contributed to the brief duration of the pauses in enrollment. Specifically, the inclusion of telephone consent in the protocol allowed clinical sites to rapidly transition to telephone consent, without protocol amendments. With support from the Methods Centre, clinical sites determined local logistics and obtained rapid ethics approval for telephone consent scripts and procedures. Enrollment decreased from 272 participants in February 2020 to a low of 47 participants in April 2020 in the closed fracture cohort. Enrollment decreased from 32 participants in February 2020 to a low of nine participants in April 2020 in the open fracture cohort. Although enrollment was significantly reduced in March, April and May 2020 in the closed fracture cohort and March and April 2020 in the open fracture cohort, all sites resumed enrollment by July 2020. Despite experiencing changes in the absolute number of participants enrolled from March to May 2020, the use of telephone consent also did not affect the percentage of eligible participants who enrolled in the trial. Given the short duration that enrollment was affected, COVID-19 had minimal impact on overall enrollment and project timelines. We stratified our analyses by open fracture versus closed fracture because these represent two distinct patient populations, and effectiveness of the PREPARE trial interventions will be assessed separately for each cohort, as described in the protocol [4].

Limitations of our findings include the exclusion of some participating clinical sites from our monthly enrollment analysis. To be included, sites must have had at least eight full months of enrollment prior to the COVID-19 pandemic. Additionally, weather and seasonality are associated with differing risks and incidence of fractures [5,6] and can, therefore, influence enrollment. However, no adjustments in our analysis were made to control for these variables. We also acknowledge that this was also a very low-risk study comparing an element of treatment that patients generally do not have a say in determining. The impact of findings related to consent in a study like this may not be generalizable to trials that evaluate new treatments with a higher risk profile.

Pragmatic trials are gaining momentum [7] because they are simple to conduct and their findings are highly generalizable. A secondary and unintended benefit uncovered by conducting a pragmatic trial during a pandemic is that they may be less prone to disruptions in the presence of an epidemic in comparison to explanatory trials. By following a pragmatic design that pre-emptively included telephone consent in the PREPARE protocol, the PREPARE trial experienced minimal interruptions to enrollment during the COVID-19 pandemic. With COVID-19 anticipated to become endemic, pragmatic designs can be used by researchers to mitigate the risk of COVID-19 transmission.
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