Rationale and Design of the Awake Prone Position for Early Hypoxemia in COVID-19 Study Protocol
A Clinical Trial

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Abstract

The unprecedented public health burdens of coronavirus disease (COVID-19) have intensified the urgency of identifying effective, low-cost treatments that limit the need for advanced life support measures and improve clinical outcomes. However, personal protective equipment and staffing shortages, disease virulence, and infectivity have created significant barriers to traditional clinical trial practices. We present the novel design of a pragmatic, adaptive, multicenter, international, prospective randomized controlled clinical trial evaluating the safety and effectiveness of awake prone positioning in spontaneously breathing patients with COVID-19 (APPEX-19 [Awake Prone Position for Early Hypoxemia in COVID-19]). Key innovations of this trial include 1) a novel smartphone-based communication process that facilitates rapid enrollment and intervention delivery while allowing social distancing and conservation of personal protective equipment, 2) Bayesian response-adaptive randomization to allow preferential assignment to the most effective intervention and expedite trial completion compared with frequentist designs, 3) remote electronic collection of patient-reported outcomes and electronic medical record data, and 4) pragmatic prospective use of patient-reported data and data collected as part of routine clinical care. Clinical trial registered with www.clinicaltrials.gov (NCT04344587).

Keywords: prone position; Bayesian analysis; COVID-19

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This article has an online supplement, which is accessible from this issue’s table of contents at www.atsjournals.org.
The coronavirus disease (COVID-19) pandemic has strained healthcare systems worldwide and is responsible for high rates of hospitalization, acute respiratory distress syndrome (ARDS), mechanical ventilation, and death (1, 2). One in four patients hospitalized with COVID-19 require transfer to the intensive care unit (ICU) and mechanical ventilation (3, 4), of whom ~40% may die before leaving the hospital (5). In addition, patients with COVID-19 admitted to the ICU may require prolonged hospitalizations with the increased use of scarce resources, resulting in shortages of trained staff, ventilators, and ICU beds (6, 7). Rapid, effective, low-cost, and universally implementable clinical interventions that reduce the need for ICU transfer and mechanical ventilation among patients with COVID-19 are urgently needed.

Prone positioning, placing a patient with the stomach and chest facing down against the bed, reduces mortality in mechanically ventilated patients with severe ARDS (those with a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen of less than 150 mm Hg) (8–10). As a result, prone positioning is recommended as the standard of care among critically ill patients with severe ARDS with (11) and without COVID-19 (12). However, prone positioning has not been shown effective among mechanically ventilated patients with mild-to-moderate ARDS (13). Although small case series and cohort studies have suggested that prone positioning among awake, spontaneously breathing patients with COVID-19 who are not receiving mechanical ventilation is generally well tolerated and associated with transient improvement in oxygenation (14–17), the effectiveness of early prone positioning at reducing the progression of COVID-19 pneumonia among nonmechanically ventilated patients remains largely unknown. Determining the effectiveness of awake prone positioning in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection requires a randomized control trial. However, conducting a clinical trial during the COVID-19 pandemic presents several unique challenges: 1) approaching patients for consent potentially exposes research personnel to infection and uses scarce personal protective equipment (PPE), 2) unpredictable epidemiology necessitates the ability to rapidly enroll and randomize patients in real time in multiple geographic regions at once, and 3) results and subsequent implementation of effective therapies are needed as soon as possible.

The APPEX-19 (Awake Prone Position for Early Hypoxemia in COVID-19) trial is a novel, pragmatic, adaptive, multicenter, international, unfunded randomized controlled trial designed by a volunteer consortium of investigators from healthcare centers across the United States to evaluate the safety and effectiveness of self–prone positioning in preventing respiratory deterioration and transfer to the ICU in awake, spontaneously breathing patients with confirmed or suspected COVID-19. APPEX-19 uses a novel smartphone-based communication process that allows for remote consent, implementation of intervention protocols, and collection of data, minimizing exposure to study personnel and use of PPE. Herein, we describe the methodology and protocol for APPEX-19, focusing on its ability to operate in the unique environment of a global pandemic.

Methods

Objectives

APPEX-19 is designed to accomplish the following objectives:

1. Evaluate the safety and effectiveness of self–prone positioning in reducing rates of respiratory deterioration and ICU transfer among awake, spontaneously breathing hospitalized patients with confirmed or suspected COVID-19. We hypothesize that self–prone positioning will reduce the rate of respiratory deterioration and ICU transfer compared with usual care.
2. Explore effects of self–prone positioning on subjective dyspnea, hospital length of stay, development of ARDS, need for mechanical ventilation, and hospital mortality among awake spontaneously breathing patients with confirmed or suspected COVID-19.
3. Identify adverse events associated with prone positioning, including patient discomfort and intravenous and urinary catheter dislodgement among awake, spontaneously breathing patients with confirmed or suspected COVID-19.
4. Rapidly implement self–prone positioning if found to be effective.
5. Function in a pandemic environment that precludes the use of traditional clinical trial enrollment methods.

Study Population

Participants in APPEX-19 are recruited from the emergency departments and medical wards of 10 healthcare systems across the United States and Spain. Eligible patients are English-speaking or Spanish-speaking adults with confirmed or suspected COVID-19 who are admitted to the medical wards or who are planned for admission to the medical wards. The decision to include patients suspected of having COVID-19 is to allow enrollment within 24 hours of admission for patients at healthcare systems that do not have access to rapid diagnostic testing and to include patients who have a high suspicion of having COVID-19 with potentially false-negative testing results.

The definition of confirmed and suspected COVID-19 is determined by individual sites to reflect the rapidly changing understanding of the signs and symptoms of COVID-19 and site-specific testing regulations. Eligible patients must be awake and spontaneously breathing room air or receiving less than 6 L/min of supplemental oxygen via a nasal cannula or nasal pendant. We exclude patients who have medical contraindications to self-proning, who are unable to self-prone, or who are unable to follow the study protocol. Complete inclusion and exclusion criteria are shown in Table 1.

Research personnel are encouraged to approach patients for recruitment and enrollment by calling the in-room telephone or the patient’s personal electronic device or when entering the room specifically for medical care, thus limiting the risk of exposure and the use of PPE. Consent is completed remotely where possible, using either a witness or an electronic consent form sent to the patient’s smartphone device. Participants in both study arms are informed of the purposes of the study, including the potential benefits of prone positioning.

Potential hurdles to the remote enrollment procedures include the inability to reach a patient by their in-room telephone or personal electronic device and the difficulty navigating electronic consent forms. To help mitigate the effect of these potential hurdles on enrollment, patients’ phones can be called multiple times when there is no answer on the initial call, wards’ front desks can be contacted by study team personnel to ensure that in-room telephones are functioning as intended, and patients with difficulty navigating the electronic consent form can be switched to a remotely witnessed paper consent form.
Participants also have the opportunity to lie in bed in whichever position is most comfortable and to keep track of the time spent in different body positions while in bed as well as an option to review the instructions. Participants also have the opportunity to review intervention instructions each time the twice-daily monitoring survey is sent to their smartphone while they are enrolled in the study.

### Study Interventions

Newly randomized participants receive a smartphone text message containing a link to a Qualtrics (Qualtrics XM)-based welcome message respective to their assigned study arm. These materials are provided in English or Spanish on the basis of the participant’s preferred language for reading. The welcome message for participants randomized to the self-prone-positioning arm contains 1) an overview of the potential benefits of prone positioning in COVID-19; 2) a recommendation to lie in the prone position for up to 12 hours per 24-hour period (up to four times daily for 1–2 h each time and at night for as long as possible); 3) a “how-to” pictorial guide to self-prone positioning in a hospital bed (Figure 1); 4) instructions to keep track of the time spent in different body positions while in bed as well as the time spent sitting upright, standing, and walking; and 5) an option to review the instructions. The welcome message for participants randomized to the usual-care arm contains instructions to lie in bed in whichever position is most comfortable and to keep track of the time spent in different body positions while in bed as well as an option to review the instructions.

### Randomization

The pragmatic Bayesian-adaptive design of APPEX-19 allows rapid testing of the effectiveness of self-prone positioning and ensures that the greatest number of participants will receive the treatment that appears most effective. The adaptive design will “bet the winner” such that more participants will be enrolled over time to the most effective treatment arm. Thus, at the conclusion of APPEX-19, both the effectiveness and the implementation of self-prone positioning via a smartphone-based recommendation can be accomplished. Randomization occurs at the time of study enrollment. The allocation sequence is concealed from study personnel. Given the nature of the intervention, participants, study personnel, and clinicians are not blinded to study-arm assignment.

### Clinical Outcomes

The primary outcome is the composite of respiratory deterioration, defined as a sustained increase in the supplemental oxygen delivery rate (≥2-L/min increase compared with the delivery rate at the time of the initial intervention sustained for at least 12 h) or the switch to a different oxygen delivery method (e.g., a transition from the nasal cannula to a nonrebreather mask, high-flow nasal cannula, noninvasive positive pressure ventilation, or mechanical ventilation) or ICU transfer. This composite primary outcome was chosen over

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**Table 1. APPEX-19 inclusion and exclusion criteria**

| Category            | Criterion                                                                 |
|---------------------|---------------------------------------------------------------------------|
| **Inclusion criteria** |                                                                            |
| Age, yr             | ≥18                                                                      |
| Location            | Admitted to medical wards in the last 24 h                              |
| COVID-19 status     | Confirmed or under investigation                                         |
| Electronics         | Smartphone with functioning internet and texting capabilities            |
| Language            | Read simple instructions and answer simple questions in English or Spanish|
| **Exclusion criteria** |                                                                            |
| Mobility            | Inability to operate the hospital bed                                   |
|                     | Inability to lie flat comfortably                                        |
|                     | Unstable spine, femur, or pelvic fracture                                |
|                     | Hemoptysis in the last 2 d                                              |
|                     | Lung transplantation                                                     |
|                     | Dementia                                                                  |
|                     | Deep venous thrombosis with blood thinners initiated within the last 2 d |
|                     | Chest tube currently in place                                            |
|                     | Tracheal surgery or sternotomy in the last 15 d                          |
|                     | Facial trauma or facial surgery in the last 15 d                         |
|                     | Cardiac pacemaker insertion in the last 2 d                             |
|                     | Known active pregnancy or no negative pregnancy test in women <50 yr    |
|                     | Receiving ≥6 L/min of supplemental oxygen via nasal cannula, nasal pendant, or shovel mask or receiving supplemental oxygen via more aggressive delivery methods (nonrebreather mask, high flow, mechanical ventilation) |
|                     | Comfort measures only                                                    |
|                     | Prisoner                                                                 |
|                     | Previous enrollment in APPEX-19                                          |

**Definition of abbreviations:** APPEX-19 = Awake Prone Position for Early Hypoxemia in COVID-19; COVID-19 = coronavirus disease.
Clinical Study Design

CLINICAL STUDY DESIGN

APPEX-19

“Prone” yourself while in the hospital bed can be safely done
using the following steps:

1) Make sure you have NOT eaten any food in the last 30 minutes and
that your call-button and smartphone are within reach

2) Lower the head of your hospital bed by pressing the down arrow on your
bed

3) Being careful to not loosen any wires or tubes that you are connected to,
genly lay yourself down on the bed with your stomach and
chest facing down.

Three different “prone” positions are shown in the images below.

You should choose the “prone” position that is most comfortable for you.
Feel free to switch between positions to remain comfortable.

APPEX-19

4) Stay in the prone position for as long as you are comfortable.
It may be helpful to listen to music or watch television as a distraction

APPEX-19

3) If at any point you become uncomfortable or are having a
difficult time breathing, you may slowly return back to lying on
your back

APPEX-19

To remind yourself, set alarms on your phone for 10AM, 1PM, 4PM, and 7PM.
During the day, try to “prone” 4 times for 1 to 2 hours each time.
At night try to “prone” for the entire night if it is comfortable to do so.

Figure 1. The “how-to” pictorial guide to self-prone positioning in a hospital bed. A step-by-step instructional guide on how to position oneself in the prone position sent to intervention-treatment-arm participants via text message. APPEX-19 = Awake Prone Position for Early Hypoxemia in COVID-19; COVID-19 = coronavirus disease.

other outcome measurements (including the World Health Organization COVID-19
10-point ordinal scale) to specifically measure if the intervention can prevent clinically
relevant respiratory deterioration and use of ICU resources. The cutoff of 6 L/min was
chosen after consultation with study site clinicians who believed there may not be
 equipoise for patients on higher amounts of supplemental oxygen. The secondary
outcomes are divided into effectiveness, safety, and self-reported compliance outcomes
(Table 2). Outcome data are ascertained via
daily electronic medical record (EMR) review
and via twice-daily, Qualtrics-based
monitoring surveys sent as text-message links
to each participant’s smartphone. Monitoring
surveys are sent until the patient reaches the
primary outcome, the patient is discharged
from the hospital, or 14 days have passed since randomization. EMR data are obtained until
discharge from the hospital or 14 days have
passed since randomization.

Site Recruitment
This study was designed by a volunteer
consortium of investigators from healthcare
centers and medical schools across the United
States recruited by social media (18). In April
2020, the response to a frequently retweeted
message revealed that multiple centers across
the United States had independently initiated
similar local trials of awake prone positioning.
After discussions conducted by web
conferencing, we arrived at a uniform awake
prone-positioning protocol. Additional sites
continue to be recruited with social media and
posting to websites for COVID-19 research
collaborations (19).

Human Subjects Research Approvals
Unlike most traditional intervention and drug
clinical trials, there is no sponsor or centralized institutional review board (IRB) for APPEX-19. Individual IRBs reviewed at each study site using a joint protocol—allowing for
modifications to the research personnel,
consent, and data-handling processes to satisfy
local policies—streamlined the review and
approval process. In addition, a central
coordinating IRB was believed to be infeasible
given the dramatic increase in workload and
IRB review requests in the setting of
COVID-19.

Data Coordinating Center
Although no central IRB exists for APPEX-19,
data collection is coordinated centrally at
Boston University. Each study site retains
master lists linking their own patient
identifiers to study identifiers and enters daily
EMR data in limited form into a central
Research Electronic Data Capture database
hosted at Boston University (20, 21). Research
Electronic Data Capture is a secure, web-based
software platform designed to support data
capture for research studies, providing 1) an
intuitive interface for validated data capture, 2) audit trails for tracking data manipulation and
export procedures, 3) automated export
procedures for seamless data downloads to
common statistical packages, and 4) procedures for data integration and
interoperability with external sources.
Monitoring survey data is remotely captured
in real time into a centralized Qualtrics-based
database. Limited Health Insurance
Portability and Accountability Act (HIPPA)
identifiers are shared between study sites.

Trial Oversight
An independent data safety monitoring board
(DSMB) composed of two pulmonary critical
care physicians and a statistician provides
oversight of participant safety during the trial.
Adverse events are monitored using the twice-
daily monitoring surveys and daily EMR.
Table 2. APPEX-19 outcomes

| Outcome                                      | Definition                                                                 |
|----------------------------------------------|---------------------------------------------------------------------------|
| **Primary effectiveness**                    | Composite of respiratory deterioration, defined as an increase in the supplemental oxygen delivery rate (≥2-L/min increase compared with the delivery rate at the time of the initial intervention sustained for at least 12 h) or the switch to a different oxygen delivery method (e.g., a transition from a nasal cannula to nonbreather mask, high-flow nasal cannula, noninvasive positive pressure ventilation, or mechanical ventilation) or ICU transfer |
| **Secondary effectiveness**                  | Self-reported modified Borg Dyspnea Score (12-point ordinal scale)         |
| – Dyspnea                                    | Need for invasive mechanical ventilation                                 |
| – Invasive mechanical ventilation            | Discharge status as reported on discharge summary                         |
| **Secondary safety**                         | Self-reported level of discomfort when lying prone (4-point ordinal scale) |
| – Discomfort                                 | Self-reported loss of intravenous catheter access as a consequence of repositioning in bed |
| – Loss of intravenous catheter               | Self-reported loss of urinary catheter access as a consequence of repositioning in bed |
| – Hospital mortality                         | Self-reported estimated time spent lying prone position (categories of no time, up to 6 h, 6–11 h, 12 h or more) |
| – Secondary compliance                       | Self-reported estimated time spent lying supine in bed, lying on the side in bed, sitting in bed, and standing or walking (categories of no time, up to 6 h, 6–11 h, 12 h or more) |

**Definition of abbreviations:** APPEX-19 = Awake Prone Position for Early Hypoxemia in COVID-19; COVID-19 = coronavirus disease; ICU = intensive care unit.

review. Adverse events and outcomes are submitted weekly to the DSMB for review. In addition to the predefined stopping criteria for overwhelming superiority or futility (online supplement), the DSMB may recommend stopping the study if evidence emerges that the risks of continuing the study outweigh the potential benefits.

**Statistical Analysis**

The primary analysis will be a modified intention-to-treat design in which participants who are randomized but discharged from the hospital or transferred to the ICU before receiving the first intervention text message are excluded.

Because of the pragmatic trial design, participants in the usual-care arm can choose to lie in the prone position, and those in the prone-position arm may refuse to lie in the prone position. Therefore, we will perform a secondary per-protocol analysis comparing participants in the intervention arm who report prone positioning for 6 or more hours on at least one survey to participants in the usual-care arm who, on all completed surveys, report fewer than 6 hours (the lowest category of self-reported prone-positioning duration) of prone positioning. In the per-protocol analysis, we will adjust for patient factors of age, sex, baseline Sequential Organ Failure Assessment score (22), baseline oxygen saturation as measured by pulse oximetry, baseline oxygen flow rate, and baseline SARS-CoV-2 test results.

Statistical analyses for the primary endpoint will be conducted using a statistical test for superiority of proportions based on posterior probability. Within each treatment group, a β (12, 28) prior will be assumed for the true primary endpoint rate. This prior was selected to express a priori skepticism of the alternative hypothesis being true; indeed, under this prior, the prior probability of the alternative hypothesis (i.e., prone positioning will improve the primary outcome rate) is 50%, whereas the probability of observing an improvement in the true rate of the primary outcome of 10.5% or higher (the hypothesized improvement) is 15%. Thus, a reversal in the prior skeptical stance will have to be only due to strong support for prone positioning in the data collected during the study. With this choice regarding the prior distribution, in each group, the posterior probability distribution of the primary outcome rates will be β (12 + number of events, 28 + number of nonevents). The criterion for success is based on the posterior probability of the alternative hypothesis (i.e., of superiority being met). The self–prone-positioning group will be declared superior to the usual-care group if the posterior probability of the alternative hypothesis Hₐ is large; that is, if

\[ P(Hₐ/\text{Data}) = P(\piₐ - \piₜ < 0/\text{Data}) > δₐ, \]

where \( \piₐ \) is the primary outcome rate in the self–prone-positioning group and \( \piₜ \) is the primary outcome rate in the usual-care group. Similarly, the self–prone-positioning group will be declared inferior to the usual-care group if the posterior probability is as follows:

\[ P(\piₜ - \piₐ < 0/\text{Data}) < 1 - δₜ, \]

The thresholds, \( δₜ \) and \( δₐ \), are prespecified levels of evidence we require to declare the alternative hypothesis true. The thresholds will be selected such that the overall type I rate for testing the primary hypothesis of superiority is bounded by 10%.

We will perform the following subgroup analyses to assess the homogeneity of the treatment effect: 1) participants with a body mass index ≥ 30 kg/m², 2) participants with an age ≥ 65 years, 3) participants with a history of congestive heart failure, 4) participants receiving supplemental oxygen at the time of enrollment, 5) participants with opacities or infiltrates on the initial chest radiograph, and 6) participants with a positive SARS-CoV-2 test result.

**Sample Size Estimates**

Based on baseline rates of the outcome identified before trial start at planned study sites, the results from randomized control trials of patients with ARDS (10), and the estimated improvement in oxygenation from early studies of awake prone positioning during COVID-19 (23), the assumptions for the sample size calculation are that the true primary outcome rate in the self–prone-positioning group is 24.5%, the true primary outcome rate in the usual-care group is 35.0%, and the power is 86.3%. A maximum total of 560 subjects will have 90% power to reject the null hypothesis (self–prone positioning will
have a primary endpoint rate equal to or exceeding that of usual care) in favor of the alternative. Because we are using the adaptive assignment and included the possibility of early stopping for overwhelming futility or superiority, the groups’ sizes are a function of the data and are therefore random. Under the alternative hypothesis, it is expected that at the time when the decision is made to stop the study, the median group size will be 173 in the self-prone-positioning group and 113 in the usual-care group. Thus, if self-prone positioning is superior to usual care, more participants will be treated with the more effective treatment. The one-sided type I error estimate is 9.3%. Additional operating characteristics are presented in Table 3.

### Trial Status
Patients are currently being enrolled in APPEX-19 at nine clinical sites across the United States, comprising Boston University (Boston Medical Center), Creighton University Medical Center, MedStar Georgetown University Hospital, National Jewish Health, the Michael E. DeBakey Veterans Affairs Medical Center, the University of Michigan (Michigan Medicine), Piedmont Healthcare Atlanta, the University of Iowa Hospital and Clinics, and the University of Kansas Medical Center, and at one international site in Madrid, Spain: the Hospital Universitario La Paz. Additional sites in the United States and Argentina are in the process of obtaining approval to begin enrollment, and the study investigators are actively seeking additional collaborators by using social media. At the time of submission, 251 patients have been enrolled since April 25, 2020.

### Discussion
Treatments for COVID-19 that improve clinical outcomes and reduce the need for advanced respiratory support are desperately needed. However, the pandemic has created unique challenges for the testing and evaluation of novel therapies (24). The APPEX-19 trial is uniquely designed to overcome the challenges of conducting a clinical trial in a pandemic setting through several innovations: 1) remote study operation—including the use of innovative smartphone-based consent, enrollment, intervention, and data collection processes—decreasing the risk of study personnel acquiring COVID-19 and eliminating the use of scarce and limited PPE resources; 2) adaptive randomization that randomizes more participants to the intervention found to be most effective; and 3) recruitment of additional study sites using social media. In addition, the virtual design elements allowed rapid scaling across centers and limited the need for a large number of study staff for enrollment and data entry (25). This ongoing protocol highlights the feasibility and efficiency of a digital randomized pragmatic trial protocol that minimizes face-to-face encounters in a pandemic setting.

### Limitations
Because pragmatic clinical trials are often embedded within routine clinical care, they may produce generalizable effect estimates and facilitate the implementation of effective novel interventions (26). Thus, if self-proning is found to be effective, the APPEX-19 protocol lends itself to translation into practice. However, pragmatic trials have limitations (27). First, the APPEX-19 intention-to-treat analysis may underestimate potential treatment effects of prone positioning if adherence is poor or if there is substantial crossover between study arms, particularly as healthcare providers may plausibly encourage more patients to self-prone as effectiveness data accrue. Subjects randomized to the control arm may be at risk for suggestion bias due to the consenting process disclosing a hypothesis of improved outcomes with prone positioning, potentially resulting in a bias toward the null. To quantify the risk of these biases, participant-reported time spent in the prone position for both the intervention group and the control group will be collected. Another limitation is that the protocol uses a centralized randomization order as opposed to randomization stratified by participating sites. As a result, the time of patient enrollment may affect the proportion of intervention or control assignments at a given participating site that would otherwise exist with individual site randomization. This limits the ability to compare intervention effectiveness within and across institutions. Finally, with respect to the primary outcome of the increase in oxygen delivery, we are unable to determine whether increases in the oxygen supplementation flow rate are due to clinical worsening or are provided to facilitate increased activity (e.g., physical therapy participation). However, the requirement that increased supplemental oxygen flow rates must be sustained for at least 12 hours helps to mitigate the risk for outcome misclassification.

APPEX-19 is a novel, pragmatic, adaptive, multicenter, international, randomized controlled trial assessing the effectiveness of early prone positioning in reducing respiratory deterioration in patients with COVID-19. This protocol incorporates several innovative design elements that best achieve the study aims efficiently and remotely during a global pandemic.

### Table 3. Operating characteristics of the proposed design

|                               | Under the Alternative Hypothesis | Under the Null Hypothesis |
|-------------------------------|----------------------------------|---------------------------|
| Self-prone positioning, true rate of primary outcome, % | 24.5                             | 35.0                      |
| Usual-care, true rate of primary outcome, %           | 35.0                             | 35.0                      |
| Stopping probability for the self–prone-positioning group, % | 86.3                             | 8.0                       |
| Stopping probability for the usual-care group, %     | 0.0                              | 1.3                       |
| Median self–prone-positioning predicted group size   | 173                              | 271                       |
| Median usual-care predicted group size               | 113                              | 271                       |

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