Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
COVID-19 SERIES

Understanding how deferred consent affects patient characteristics and outcomes: an exploratory analysis of a clinical trial of prone positioning for COVID-19

Michael Colacci, Afsaneh Raissi, Ajay Bhasin, Leora Branfield Day, Melissa Bregger, Travis Carpenter, Lana Castellucci, Angela M. Cheung, Laura Dragoi, Richard Dunbar-Yaffe, Lee Fidler, Rob Fowler, Alexi Gossel, Rachel Hensel, Margaret Herridge, Haseena Hussein, Moira Kapral, Laveena Munshi, Kieran Quinn, Fahad Razak, Bruno Roza da Costa, Christine Soong, Terence Tang, Kevin Venus, Amol Verma, Michael Fralick

*Corresponding author. Sinai Health System, Department of Internal Medicine, 5th Floor Room L255, 60 Murray Street, Toronto, Ontario, Canada. Tel.: +1 416 586 4800. E-mail address: fralick@mail.utoronto.ca (M. Fralick).

https://doi.org/10.1016/j.jclinepi.2022.08.017

0895-4356/© 2022 Elsevier Inc. All rights reserved.
Key findings
- Differences in characteristics were found between patients in the deferred consent and nondeferred consent groups.
- Primarily, it was found that the patients in the deferred consent group were more likely to be enrolled on weekends and were more likely to be older.

What this adds to what was known
- This finding shows that deferred consent, the process of enrolling patients in clinical trials prior to obtaining consent, may allow for the enrollment of a greater number of individuals.

What is the implication and what should change now?
- These findings may have implications for obtaining consent when conducting clinical trials in the future.

1. Introduction
Deferred consent, the process of enrolling patients in a clinical trial before consent is obtained, is often employed in studies of minimal risk [1–4], or when patients are unable to consent at the time of study enrollment [5–8]. Deferred consent has several possible benefits including decreasing the time to study enrollment, allowing for enrollment when study personnel are unavailable [9,10], and allowing the inclusion of populations less represented in clinical trials [4,11,12]. Multiple studies have identified that deferred consent is considered an acceptable substitute for pre-enrollment consent by both participants and clinicians [13,14]. Our objective was to assess patient-level characteristics, adherence, and rate of withdrawal among participants enrolled with consent obtained before (nondeferred consent) vs. after (deferred consent) randomization in the COVID-PRONE randomized trial (NCT04383613).

2. Methods
We conducted a secondary analysis of the COVID-prone international, pragmatic randomized clinical trial, which assessed prone positioning in patients with COVID-19 [15].
Deferred consent was allowed as the benefit of prone positioning was thought to be greatest when immediately implemented, because patients may be in respiratory distress at the time of enrollment, and because we expected potential harms from prone positioning to be minimal. Deferred consent was allowed at all except two hospitals. The decision on timing of consent was made by the site lead at the time of recruitment.

The primary outcome of this analysis was the difference in patient characteristics, time spent prone, and rate of withdrawal among participants who were enrolled with consent obtained before vs. after randomization. We did not compare the primary outcome between the two groups because our study was stopped for futility and our primary outcome was similar between patients randomized to prone positioning compared to standard of care.

3. Results
Among 248 total patients, 125 (50.5%) were enrolled after consent, and 123 (49.5%) were enrolled with deferred consent. The median time between randomization and consent was 1 day (interquartile range [IQR] 0–2 days) in the deferred consent group. Patients in the deferred consent group were more likely to be enrolled on weekends (14.6% vs. 9.6%), male (67.5% vs. 60.8%), and older (median age 60 vs. 54 years) Table 1. The frequency of deferred consent varied significantly by hospital (median 41.5%; range: 0–100%). Patients in the deferred consent group were more likely to require oxygen via face mask (9.8% vs. 2.4%) and less likely to have received remdesivir (27.6% vs. 56%).

There was no difference in the rates of study withdrawal ([3%] in each group) or median number of hours spent in prone position within the group randomized to prone positioning (nondeferred = 7 [IQR 2.3–16.8], deferred = 4 [IQR 1.3–12.0]). The rate of serious adverse events was 4.9% in the deferred consent group and 1.6% in the non-deferred consent group Table 2.

4. Discussion
In this secondary analysis of an international randomized controlled trial of prone positioning for noncritically ill patients with COVID-19, patients who underwent deferred consent were more likely to be male, older, and be enrolled on a weekend. We observed similar rates of both participant withdrawal and protocol adherence.

Our study has several limitations. First, data were unavailable for why deferred consent was chosen. Second, we did not ascertain patients’ and providers’ perspectives on deferred consent, though prior literature has shown that both groups find it to be an acceptable alternative [13,14]. Third, this was an exploratory and post-hoc analysis, and thus we did not test for statistical significance and our findings require replication.

Our results suggest that the use of deferred consent may allow for the inclusion of patients who would not otherwise
## Table 1. Baseline characteristics

| Characteristic                          | Deferred ($N = 123$) | Nondeferred ($N = 125$) |
|-----------------------------------------|-----------------------|--------------------------|
| **COVID status**                        |                       |                          |
| COVID-19 test result                    | 120 (97.6%)           | 122 (97.6%)              |
| **Randomization timing**                |                       |                          |
| Number of days between admission and randomization | 1 [1, 1]          | 1 [1, 1]                 |
| Days between randomization and consent  | 1 [0, 2]              | 0 [0, 0]                 |
| Randomized on a saturday or sunday     | 18 (14.6%)            | 12 (9.6%)                |
| **Age**                                 |                       |                          |
| Median [IQR]                            | 60 [49.5, 68]         | 54 [39, 61]              |
| <50                                     | 31 (25.2%)            | 50 (40%)                 |
| 50–70                                   | 69 (56.1%)            | 64 (51.2%)               |
| >70                                     | 23 (18.7%)            | 11 (8.8%)                |
| **Sex**                                 |                       |                          |
| Female                                  | 40 (32.5%)            | 49 (39.2%)               |
| **Date of randomization**               |                       |                          |
| Before Sept 1, 2020                     | 6 (4.9%)              | 2 (1.6%)                 |
| Sept 1, 2020 to Feb 28, 2021           | 84 (68.3%)            | 60 (48%)                 |
| After Feb 28, 2021                      | 33 (26.8%)            | 63 (50.4%)               |
| **Comorbid conditions**                 |                       |                          |
| Diabetes                                | 35 (28.5%)            | 32 (25.6%)               |
| Hypertension                            | 47 (38.2%)            | 51 (40.8%)               |
| Current smoker                          | 4 (3.3%)              | 3 (2.4%)                 |
| COPD or asthma                          | 8 (6.5%)              | 19 (15.2%)               |
| Heart failure                           | 3 (2.4%)              | 3 (2.4%)                 |
| **Illness severity**                    |                       |                          |
| Lymphocyte count                        | 0.82 [0.6, 1.1]       | 0.9 [0.68, 1.2]          |
| Creatinine                              | 81 [66, 100]          | 76 [63, 93]              |
| Systolic blood pressure                 | 123 [114, 133]        | 122.5 [115, 130]         |
| Oxygen saturation                       | 94 [93, 96]           | 94 [93, 95]              |
| FiO2                                    | 32 [28, 36]           | 32 [28, 36]              |
| S/F ratio                               | 303 [261, 339]        | 305 [264, 337]           |
| **FiO2 delivery method**                |                       |                          |
| Nasal prong                             | 109 (88.6%)           | 113 (90.4%)              |
| High-flow nasal cannula                 | 1 (0.8%)              | 6 (4.8%)                 |
| Face mask                               | 12 (9.8%)             | 3 (2.4%)                 |
| **Medication**                          |                       |                          |
| Dexamethasone                           | 115 (93.5%)           | 121 (96.8%)              |
| Remdesivir                              | 34 (27.6%)            | 70 (56%)                 |
| Tocilizumab                             | 0 (0%)                | 2 (1.6%)                 |
| **Code status**                         |                       |                          |
| Full code                               | 110 (89.4%)           | 119 (95.2%)              |
| Do not resuscitate                      | 5 (4.1%)              | 0 (0%)                   |
| Other                                   | 8 (6.5%)              | 5 (4%)                   |

**Abbreviations:** COPD, chronic obstructive pulmonary disease; FiO2, fraction of inspired oxygen; IQR, interquartile range; S/F ratio, ratio of saturation of oxygen to fraction of inspired oxygen.

Missingness for all variables was <2%.
have been enrolled (e.g., patients hospitalized on weekends), potentially improving the external generalizability of randomized trials.

References

[1] Grimes DA, Hubacher D, Nanda K, Schulz KF, Moher D, Altman DG. The Good Clinical Practice guideline: a bronze standard for clinical research. Lancet 2005;366:172–4.

[2] Harron K, Woolfall K, Dwan K, Gamble C, Mok Q, Ramnarayan P, et al. Deferred consent for randomized controlled trials in emergency care settings. Pediatrics 2015;136:e1316–22.

[3] Topolovec-Vranic J, Santos M, Baker AJ, Smith OM, Burns KEA. Deferred consent in a minimal-risk study involving critically ill subarachnoid hemorrhage patients. Can Respir J 2014;21:293–6.

[4] Honarmand K, Belley-Cote EP, Ulic D, Khalifa A, Gibson A, McClure G, et al. The deferred consent model in a prospective observational study evaluating myocardial injury in the intensive care unit. J Intensive Care Med 2018;33:475–80.

[5] The ARISE Investigators and the ANZICS Clinical Trials Group*. Goal-directed resuscitation for patients with early septic shock. N Engl J Med 2014;371:1496–506. https://doi.org/10.1056/NEJMoa1404380.

[6] Young P, Saxena M, Bellomo R, Freebairn R, Hammond N, van Haren F, et al. Acetaminophen for fever in critically ill patients with suspected infection. N Engl J Med 2015;373:2215–24.

[7] Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A,Gattas D, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med 2012;367:1901–11.

[8] The NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009;360:1283–97.

[9] Shamy MCF, Dewar B, Chevrier S, Wang CQ, Page S, Goyal M, et al. Deferral of consent in acute stroke trials. Stroke 2019;50:1017–20.

[10] Menon K, O’Hearn K, McNally JD, Acharya A, Wong HR, Lawson M, et al. Comparison of consent models in a randomized trial of corticosteroids in pediatric septic shock. Pediatr Crit Care Med 2017;18:1009–18.

[11] Burns KEA, Zubrinich C, Tan W, Raptis S, Xiong W, Smith O, et al. Research recruitment practices and critically ill patients: a multi-center, cross-sectional study (the consent study). Am J Respir Crit Care Med 2013;187:1212–8.

[12] Byrne MM, Tannenbaum SL, Glück S, Hurley J, Antoni M. Participation in cancer clinical trials: why are patients not participating? Med Decis Making 2014;34:116–26.

[13] Manda-Taylor L, Bickton FM, Gooding K, Rylance J. A formative qualitative study on the acceptability of deferred consent in adult emergency care research in Malawi. J Empir Res Hum Res Ethics 2019;14:318–27.

[14] Den Boer MC, Houtlosser M, Foglia EE, Lopriore E, de Vries MC, Engberts DP, et al. Deferred consent for delivery room studies: the providers’ perspective. Arch Dis Child Fetal Neonatal Ed 2020;105:310–5.

[15] Fralick M, Colacci M, Munshi L, Venus K, Fidler L, Hussein H, et al. Prone positioning of patients with moderate hypoxaemia due to covid-19: multicentre pragmatic randomised trial (COVID-PRONE). BMJ 2022;376:e068585.

Table 2. Secondary outcomes and rate of adverse events among patients enrolled with deferred vs. nondeferred consent

| Outcome                                      | Deferred (N = 123) | Non-deferred (N = 125) |
|----------------------------------------------|--------------------|------------------------|
| S/F ratio after 72 hours                     | 332 [207, 423]     | 345 [260, 446]         |
| Change in S/F ratio in first 72 hours (median [IQR]) | 7 [-58, 73]   | 60 [-20, 108]          |
| Change in FiO2 (%) in first 72 hours (median [IQR]) | 0 [-7, 8]    | -4 [-8, 4]             |
| Days to discharge (median [IQR])             | 6 [4, 10]          | 4 [3, 6]               |
| Discharged                                   | 114 (92.7%)        | 119 (95.2%)            |

**Abbreviations**: IQR, interquartile range; SAE, severe adverse event; S/F ratio, ratio of saturation of oxygen to fraction of inspired oxygen.