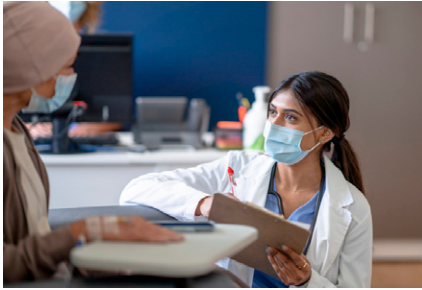


The Potential for Increasing Risk of Consent Refusal in COVID-19 Trials Considering Underlying Reasons and Responses

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Recently, we observed decreased recruitment of eligible hospitalized patients with coronavirus disease (COVID-19) into randomized controlled trials (RCTs) coincident with the observation that most patients hospitalized with severe COVID-19 are now unvaccinated.

Rigorous RCTs are fundamental to discovery of effective vaccines (1) and therapies (2) for COVID-19 and for eliminating ineffective treatment (3). RCTs that compare standard therapy with potentially incrementally better therapy are essential in advancing COVID-19 treatment. The important extensions of need for successful trials are 1) that there are still patients dying of COVID-19, and 2) that there are now recognized significant chronic complications of COVID-19 (post-COVID-19 conditions) that could be avoided with better treatments proven by rigorous trials.

Nonexperimental observational studies help but do not provide sufficient

confidence regarding efficacy and safety because observational studies can lead to false inference of effectiveness or harm. We need RCTs to expand our armamentarium of vaccines and therapies as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus mutates, increasing transmissibility and increasing or—in the case of Omicron—decreasing risks of hospitalization and death.

Vaccination effectively prevents severe COVID-19 (hospital and ICU admissions). Now, most patients with severe illness have not been fully vaccinated. Although vaccination has been less effective in preventing Omicron transmission, it appears to decrease the incidence of hospitalization. So although the genotype of COVID-19 infections is changing, this issue remains highly relevant. As of February 22, 2022, 80% of Canadians over age 12 are fully vaccinated; 84% had at least one vaccine dose (<https://health-infobase.canada.ca/covid-19/vaccination-coverage/>). Among a sample of 1,046,386 people with COVID-19 known to the Public Health Agency of Canada, 78.8% of those hospitalized and 75.4% of nonsurvivors were unvaccinated (<https://health-infobase.canada.ca/covid-19/epidemiological-summary-covid-19-cases.html>). In Ontario, as of February 22, 2022, the rate of hospital admission among those unvaccinated was 325 out of 1,000,000 compared with 55 out of 1,000,000 for people

who received at least two vaccine doses, a sixfold difference (<https://covid19-sciencetable.ca/ontario-dashboard/>); in-ICU rates are 153 out of 1,000,000 compared with 12 out of 1,000,000, respectively, a 13-fold difference.

We are conducting several COVID-19–related RCTs and have noted that refusal of consent has increased substantially. In one multicenter COVID-19 RCT (<https://clinicaltrials.gov/ct2/show/NCT04606563>), refusal of consent rates recently nearly doubled, increasing from 18% in the third quarter of 2021 to 35% in the fourth quarter of 2021, coincident with the high proportion of unvaccinated adults in the hospital in Canada.

Increased refusal of COVID-19 RCT consent is noted anecdotally among COVID-19 clinical trialists. Perhaps lessons can be learned from studies of vaccine hesitancy. COVID-19 vaccine trials emphasize elements of informed consent (4). The rate of refusal to be vaccinated is increasing across 13 countries (5). Canadian and UK studies found that 19% (6) of healthcare workers and 31% of the general population (7) did not accept vaccines (6) or were vaccine hesitant (7). Refusal of vaccine occurred because some patients thought that vaccines were too novel and that there was insufficient time to make decisions to have vaccines in healthcare workers (6); persons who refused vaccines were also less likely to get their information about COVID-19 from

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authoritative sources (7). In a French survey, more persons would agree to vaccination (75%) than would consent to join a vaccine trial (48%), highlighting the greater hesitancy for vaccine trials (8). Vaccine hesitancy occurred in 40% of Australian survey respondents. Females, the disadvantaged, those stating that risk of COVID-19 was overstated, and those with populist views and higher degrees of religiosity were more vaccine hesitant or resistant (9). Similar drivers may occur in patients who refuse consent for nonvaccine COVID-19 RCTs.

Perhaps this increase in consent refusal for COVID-19 RCTs was not unexpected. In our experience, many unvaccinated patients decline research because they may be less trustful of medicine in general. Unvaccinated patients now comprise the majority of severely ill patients with COVID-19 and are exactly the patients most in need of increasingly effective therapies, which requires new RCTs.

The broader implications of our observations are important. The incredible progress that has been made proving therapies effective against COVID-19 will slow not necessarily owing to waning numbers of hospitalized patients in need of better therapies, but because the population is decreasingly receptive to engage in clinical

research. This research hesitancy has unfortunate implications for currently infected individuals and the future population health. If COVID-19 RCT enrollment falls, trials will take longer and may be at increased likelihood of stopping early, generating longer durations to find effective therapies and more exposure to ineffective therapies.

We have begun to use strategies to address this decline in patients' consent to participate in COVID-19 research. First, we have increased awareness and training of our research staff regarding currently vulnerable populations, including those who are vaccine and research hesitant. Vulnerable populations for RCT refusal include the disadvantaged, those who limited their access to reliable information sources, and those with high religiosity (9). Second, we adjusted our research associate training to emphasize empathetic education regarding acute (high risk of ICU admission, ventilation, and death) and chronic (long COVID-19) (10) consequences of COVID-19. We have noted a lack of awareness of long COVID-19 among unvaccinated patients, and so we have updated our disclosure to patients regarding the potential risks and consequences of long COVID-19 (e.g., impaired cognition, fatigue, and dyspnea [10]). Third, we have had some

patients who were previously unvaccinated and have subsequently consented to RCTs and vaccination engage with the lay media to highlight the importance of their change of mind and heart.

Our individual case-based observations to date are that there has been modest impact of these strategies, exemplified by patients' consenting to participate in COVID-19 RCTs, agreeing to be vaccinated, and subsequently volunteering as public advocates. To our knowledge, there has been little awareness of this issue of potentially increasing research hesitancy or of strategies to effectively educate and thereby improve participation and enrollment rates in COVID-19 clinical research.

We strongly recommend that the COVID-19 research community consider this challenge and evolve additional strategies and empathetic educational methods to help unvaccinated and research-hesitant patients become aware of the benefits, as well as the risks, inherent in vaccination decisions and participation in clinical research in COVID-19. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

- 1 El Sahly HM, Baden LR, Essink B, Doblecki-Lewis S, Martin JM, Anderson EJ, *et al.*; COVE Study Group. Efficacy of the mRNA-1273 SARS-CoV-2 vaccine at completion of blinded phase. *N Engl J Med* 2021;385:1774–1785.
- 2 Malin JJ, Spinner CD, Janssens U, Welte T, Weber-Carstens S, Schälte G, *et al.* Key summary of German national treatment guidance for hospitalized COVID-19 patients: key pharmacologic recommendations from a national German living guideline using an Evidence to Decision Framework (last updated 17.05.2021). *Infection* 2022;50:93–106.
- 3 Kalil AC, Mehta AK, Patterson TF, Erdmann N, Gomez CA, Jain MK, *et al.*; ACTT-3 study group members. Efficacy of interferon beta-1a plus remdesivir compared with remdesivir alone in hospitalised adults with COVID-19: a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Respir Med* 2021;9:1365–1376.
- 4 Cardozo T, Veazey R. Informed consent disclosure to vaccine trial subjects of risk of COVID-19 vaccines worsening clinical disease. *Int J Clin Pract* 2021;75:e13795.
- 5 Robinson E, Jones A, Lesser I, Daly M. International estimates of intended uptake and refusal of COVID-19 vaccines: a rapid systematic review and meta-analysis of large nationally representative samples. *Vaccine* 2021;39:2024–2034.
- 6 Dzieciolowska S, Hamel D, Gadio S, Dionne M, Gagnon D, Robitaille L, *et al.* Covid-19 vaccine acceptance, hesitancy, and refusal among Canadian healthcare workers: a multicenter survey. *Am J Infect Control* 2021;49:1152–1157.
- 7 Murphy J, Vallières F, Bentall RP, Shevlin M, McBride O, Hartman TK, *et al.* Psychological characteristics associated with COVID-19 vaccine hesitancy and resistance in Ireland and the United Kingdom. *Nat Commun* 2021;12:29.
- 8 Detoc M, Bruel S, Frappe P, Tardy B, Botelho-Nevers E, Gagneux-Brunon A. Intention to participate in a COVID-19 vaccine clinical trial and to get vaccinated against COVID-19 in France during the pandemic. *Vaccine* 2020;38:7002–7006.
- 9 Edwards B, Biddle N, Gray M, Sollis K. COVID-19 vaccine hesitancy and resistance: correlates in a nationally representative longitudinal survey of the Australian population. *PLoS One* 2021;16:e0248892.
- 10 Dennis A, Wamil M, Alberts J, Oben J, Cuthbertson DJ, Wootton D, *et al.*; COVERSCAN study investigators. Multiorgan impairment in low-risk individuals with post-COVID-19 syndrome: a prospective, community-based study. *BMJ Open* 2021;11:e048391.