Background

The informed consent process, a metric of autonomy, confers upon participants the right to decline or accept participation in a study in equal measure.[1] An analysis of consent declines and consent withdrawals can thus serve as a useful index of the adequacy of the informed consent process.[2] As the COVID-19 pandemic continues to ravage the world, several studies have been published in this area and continue to be conducted both in patients (with repurposed or experimental treatments),[3-6] and normal healthy participants (vaccines or drugs for prophylaxis),[7-9] in an attempt to treat or mitigate the course of the disease.

ABSTRACT

Objectives: We evaluated the extent of consent declines and consent withdrawals during the COVID-19 pandemic as seen in published randomized controlled trials (RCTs) and compared it with non-COVID-19 RCTs published at the same time and two historical controls.

Methods: PubMed/Medline only was searched using key-word “COVID-19” and “RCTs” separately, and filtered for COVID-19 RCTs and non-COVID-19 RCTs respectively, published during a nine-month period (1 Feb - 1 Nov 2020). Exclusions were study protocols, observational studies, interim analysis of RCT data and RCTs with missing data. Primary outcome measures were the proportion of consent declines and consent withdrawals as percentage of total participants screened and randomized respectively in COVID-19 RCTs. We compared consent declines and consent withdrawals of COVID-19 RCTs with non-COVID-19 RCTs and two earlier studies on the same topic that served as historical controls (non-pandemic setting).

Results: The search yielded a total of 111 COVID-19 RCTs and 49 non-COVID-19 RCTs. Of these, 39 (35.13%) COVID-19 RCTs and 11 (22.45%) non-COVID-19 RCTs were finally analysed. A total of 770/17759 (4.3%) consent declines and 100/7607 (1.31%) consent withdrawals were seen in 39 COVID-19 RCTs. A significant difference was observed in consent declines between COVID-19 vs non-COVID-19 RCTs [4.3% vs 11.9%, \( p < 0.0001 \)] and between COVID-19 RCTs vs two historical controls [(4.3% vs 8.6%, \( p < 0.0001 \) ) and (4.3% vs 21.1%, \( p < 0.0001 \), respectively).

Conclusion: RCTs conducted during the COVID-19 pandemic appear to have significantly lower consent declines relative to non-COVID-19 RCTs during pandemic and RCTs conducted in non-pandemic settings.

KEY WORDS: Consent declines, consent withdrawal, COVID-19, randomized controlled trial, vaccine.
The informed consent process during a pandemic can be exceedingly difficult as patients are not likely to have access to medication, are likely to be desolate to the point of being reckless [in the face of uncertainty] and suffer from therapeutic misconception.\(^{(10)}\) They may also be too sick to give consent themselves. Their legally acceptable representatives (LAR) also may be ill themselves or quarantined when families as a cluster are affected.

Against this backdrop, a literature review of consent declines and consent withdrawals as seen in published literature [COVID-19 RCTs] can help us understand the extent to which participants decline participation or withdraw consent in clinical research during a pandemic and hence the present study was envisaged. A secondary objective was to compare the stated metrics with similar data from non-COVID-19 RCTs published during the pandemic (same time frame) as well as historical controls (studies done earlier during a non-pandemic time).

### Materials and Methods

#### Ethics

The study [EC/OA-157/2020] was accorded a waiver by Institutional Ethics Committee.

#### Case definitions used for the study

A consent decline was defined as that occurring at the time of screening,\(^{(11)}\) while a consent withdrawal was defined as one that occurred after the participant signed the informed consent document.\(^{(11)}\) Thus, the denominator for consent declines was the total number of participants screened whereas for consent withdrawals it was the total number of participants randomized.

#### Search strategy and time period

a) COVID-19 RCTs: PubMed/Medline was searched using the keywords “RCTs” AND “COVID-19” for English language publications.

b) non-COVID-19 RCTs: PubMed/Medline was searched using the keywords “RCTs”, after filtering out all COVID-19 RCTs. A nine-month time period (1 Feb - 1 Nov 2020) was chosen. The search was done independently by two authors and verified by the senior authors.

#### Selection criteria

For both types of RCTs; study protocols, observational studies, interim analysis of data, studies on e-learning for COVID-19 and RCTs where data on consent declines and consent withdrawals was missing were excluded. This gave us only RCTs with interventions for analysis.

#### Outcome measures

The primary outcome measures were a) the proportion of consent declines as a percentage of total participants screened and b) the proportion of consent withdrawals as a percentage of total participants randomized in COVID-19 RCTs. The secondary outcome measures were comparison of consent declines (and consent withdrawals where applicable) of the COVID-19 RCTs with i) non-COVID-19 RCTs and ii) two historical controls [see below]. Within a given COVID-19 RCT, we also compared the stated metrics for therapeutic versus prophylactic interventions and disease severity of COVID-19,\(^{(12)}\) (mild,\(^{(1)}\) and moderate-severe,\(^{(16)}\)). Only consent withdrawals were compared for interventional arm versus standard of care/best supportive care arms.

#### Historical controls

Two earlier studies published on a similar topic were chosen as historical controls. The first study was an analysis of consent declines amongst RCTs published in three leading, high impact factor medical journals and thus similar to the present study.\(^{(2)}\)

The second was an analysis of consent declines in ten studies conducted at a tertiary referral centre and thus disparate.\(^{(14)}\)

#### Statistical analysis

Both descriptive and inferential statistics were used. Categorical data (proportion of consent declines and consent withdrawals) are expressed as percentages. The number of consent declines and withdrawals (quantitative data) are expressed as median (range). The proportion of consent declines and consent withdrawals in COVID-19 RCTs relative to non-COVID-19 RCTs as well as the proportion of consent declines in COVID-19 RCTs relative to the historical controls were analysed using the Chi-square test. Also, the proportion of consent declines and consent withdrawals in COVID-19 RCTs with mild disease relative to those with moderate-severe disease were analysed using the Chi-square test. All analyses were done at 5% significance using Epi Info 7.0.

#### Results

##### Demographic data

As of 17th November 2020, a total of 160 RCTs were available on PubMed/Medline. Of these, 111 were COVID-19 RCTs and the remaining 49 were non-COVID-19 RCTs.

**COVID-19 RCTs**

Of the 111 RCTs, 72/111 (64.86%) were excluded. A total of 39/111 (35.13%) RCTs formed the final sample. Of these, 36/39 (92.3%) were RCTs with repurposed drugs for COVID-19 patients whereas 2/39 (5.1%) were vaccine studies and 1/39 (2.5%) was a study that used hydroxychloroquine (HCQ) as prophylaxis [in normal, healthy participants] [Table 1].

The disease severity of COVID-19 in 36/39 (92.3%) RCTs was categorized as mild (8/36, 22.2%) and moderate-severe (28/36, 77.8%).

**Non-COVID-19 RCTs**

Out of 49 RCTs, 38/49 (77.56%) RCTs were not analysed as they met exclusion criteria. A total of 11/49 (22.45%) RCTs formed the comparison group [Table 1].

#### Analysis of consent declines and consent withdrawals

**COVID-19 RCTs**

A total of 770/17759 (4.3%) consent declines and 100/7607 (1.31%) consent withdrawals were seen in 39/39 and 37/39 RCTs respectively [Table 2]. The median (range) consent declines and consent withdrawals were 2 (0-238) and 1 (0-19) respectively.
Non-COVID-19 RCTs
Among 11 (22.45%) RCTs, total consent declines and consent withdrawals noted were 1172/9867 (11.9%) and 102/6155 (1.65%) respectively [Table 2].

Comparison of consent declines and consent withdrawals in COVID-19 RCTs vs non-COVID-19 RCTs
A statistically significant difference was seen between the two groups with fewer consent declines in the COVID-19 RCTs [4.3% vs 11.9%, \( p < 0.0001 \)]. On the contrary, the consent withdrawals between two groups were not statistically significant [1.31% vs 1.65%, \( p = 0.11 \)] [Table 2].

Comparison of consent declines in COVID-19 RCTs with historical controls
When the consent declines in COVID-19 RCTs were compared with the first historical control (consent declines in RCTs published in three leading biomedical journals), it was seen that there was a statistically significant difference between the two groups with fewer consent declines seen in COVID-19 RCTs [4.3% vs 8.6%, \( p < 0.0001 \)]. Likewise, fewer consent declines were seen in COVID-19 RCTs relative to another historical control that evaluated consent declines in \( n = 10 \) studies at a tertiary centre. The consent decline rate of 4.3% with the former was much less than the consent decline rate of 21.1% with the latter [\( p < 0.0001 \)] [Table 2].

Miscellaneous analysis
Consent declines and consent withdrawals in COVID-19 RCTs based on disease severity
When the consent declines and consent withdrawals in COVID-19 RCTs with mild disease relative to those with moderate-severe disease were compared, a statistically significant difference was seen with fewer consent declines and consent withdrawals in the those with mild disease relative to moderate-severe disease, [0.4% vs 4.53%, \( p < 0.001 \)] and [0.2% vs 1.85%, \( p < 0.0001 \)] respectively.

Comparison of consent withdrawals in the standard of care/best supportive care vs interventional arms in COVID-19 RCTs
A total of 100/7607 participants (1.31%) withdrew consent in 37/39 RCTs. Consent withdrawals were 0.8% in the standard of care/best supportive care arm vs 1.34% in interventional arm [\( p = 0.01 \)].

Nature of study and extent of consent declines and consent withdrawals in COVID-19 RCTs
In 36/39 (92.3%) therapeutic RCTs, a total of 352/10466 (3.4%)

Table 1: Demographic Data of Randomized Controlled Trials (RCTs) in the Present Literature Review (COVID-19 and non-COVID-19 RCTs)

| Reasons for Exclusion | Total No. of RCTs Available in PubMed/Medline (N=160) |
|-----------------------|-----------------------------------------------------|
| Consent declines or consent withdrawals not available | COVID-19 RCTs (N=72/111) [n/N (%)] 28 (25.22) non-COVID-19 RCTs (N=38/49) [n/N (%)] 27 (55.1) |
| Study protocols | 27 (24.32) 5 (10.2) |
| Observational studies | 6 (5.4) 2 (4.08) |
| Studies with simulations and e-learning modules for COVID-19 | 5 (4.5) - |
| Study conducted outside inclusion date | 3 (2.7) - |
| Preliminary/Interim publications | 2 (1.8) 1 (2.04) |
| Meta-analysis | - 3 (6.12) |

| Reasons for inclusion | COVID-19 RCTs (N=39/111) [n/N (%)] 36/39 (92.3) non-COVID-19 RCTs (N=11/49) [n/N (%)] 6/11 (54.5) |
|-----------------------|-----------------------------------------------------|
| Therapeutics | 36/39 (92.3) 6/11 (54.5) |
| Prophylaxis | 3/39 (7.69) 5/11 (45.5) |

| Proportion of consent declines and consent withdrawals in present literature review | COVID-19 RCTs (N=39) [n/N (%)] 770/17759 (4.3) non-COVID-19 RCTs (N=11) [n/N (%)] 1172/9867 (11.9) |
|-----------------------|-----------------------------------------------------|
| Consent declines | 1172/9867 (11.9) |
| Consent withdrawals | 100/7607 (1.31) 102/6155 (1.65) |

Note: One study entirely in Spanish was excluded. Simulation study was a problem-based learning among nursing students whereas e-learning module was a web based RCT on personal protective equipment proficiency. Both did not include drug or vaccine related to COVID-19 and hence were excluded.

Table 2: Analysis of Consent Declines and Consent Withdrawals in Present Literature Review (COVID-19 And non-COVID-19 RCTs) And Two Historical Controls

| Present literature review (COVID-19 RCTs) | Present literature review (non-COVID-19 RCTs) | Historical control 1,[2] | Historical control 2,[14] |
|------------------------------------------|-------------------------------------------|-----------------------|-----------------------|
| Total no. of consent declines [n/N (%)] | 770/17759 (4.3) | 1172/9867 (11.9) | 3,22,271/37,53,700 (8.6) | 206/976 (21.1) |
| Total no. of consent withdrawals [n/N (%)] | 100/7607 (1.31) | 102/6155 (1.65) | Not available | Not available |

Note: *Comparison of Consent Declines in COVID-19 vs non-COVID-19 RCTs, †Comparison of Consent Declines in COVID-19 RCTs vs Historical Control 1, ‡Comparison of Consent Declines in COVID-19 RCTs vs Historical Control 2, §Comparison of Consent Withdrawals in COVID-19 RCTs vs non-COVID19 RCTs, \( p < 0.05 \) is considered statistically significant
consent declines and 82/5216 (1.6%) consent withdrawals were noted. Similarly, 240/7293 (3.3%) consent declines and 8/2406 (0.34%) consent withdrawals were noted in 3/39 (7.6%) RCTs that had prophylactic interventions. Some RCTs had a zero percent consent decline rate (one vaccine trial and 14 trials with repurposed drugs), while others such as Hydrocortisone in severe COVID-19, and HCQ prophylaxis, had a much higher consent declines at 16% and 5% respectively.

Discussion

The present literature review evaluated consent declines and consent withdrawals in published COVID-19 RCTs (PubMed/ Medline only) and showed a much lower consent decline rate in these studies (4.3%) relative to non-COVID-19 RCTs during a pandemic (11.9%) and the two historical controls (audits) conducted in a non-pandemic setting at 8.6% and 21%, respectively indicating that participants are less likely to decline consent in COVID-19 RCTs conducted during the pandemic.

In COVID-19, to date, there is no effective anti-viral drug and treatments are largely repurposed. In many countries, depending upon the status of patents on these repurposed drugs (for example: Remdesivir, Sofosbuvir); patients may or may not be able to afford the treatment. Thus, clinical research remains the best opportunity to access these treatments.

The consent declines (11.9%) in non-COVID-19 RCTs are almost thrice that of 4.3% as seen in COVID-19 RCTs during a pandemic. This strengthens our hypothesis of desperation, lack of access to medication and therapeutic misconception which may have contributed to lower consent declines in COVID-19 RCTs.

In the present literature review, consent declines in mild COVID-19 disease (0.4%) were found to be almost four times lower than those with moderate-severe disease (4.53%). Similarly, fewer consent withdrawals were noted in mild COVID-19 disease (0.2%) relative to those with moderate-severe disease (1.85%). This finding is not very easy to explain. One possibility is that with mild disease, the decision making was done by the patient himself while with moderate and severe disease, both patients and LARs may have been involved in the decision making leading to the difference seen.

Both historical controls were audits at our centre which is a high-volume research facility at a tertiary referral hospital in Western India. The first historical control was an evaluation of consent declines in RCTs (as seen in the CONSORT flow charts) published in three leading biomedical journals which is a better control for the present literature review as it is on similar lines. The consent decline rates of 8.6% are twice that of 4.3% as seen in COVID19 RCTs in a pandemic setting reaffirming the fact that consent declines indeed seem lower in a pandemic. The second historical control was an audit where analysis of consent declines in ten studies was conducted at our centre. Here, the nature of studies were phase I-IV studies with pharmacokinetic, safety, efficacy and bioequivalence analysis (three observational and seven interventional) which showed a consent decline rate of 21.1%, ranging from 0-64%. This is both a strength (done during a non-pandemic setting) and a limitation (not all studies were RCTs) of the second historical control.

While the overall consent decline rate in COVID-19 RCTs was 4.3%, it ranged from 0-16%. Zero consent declines were seen in one vaccine RCT among the 39 studies. This indicates either desperation or therapeutic misconception as a possible cause. Contrary to this, Li et al., in a phase 1 trial (China, single centre) for a vaccine during Ebola epidemic found 11% consent declines and 8.4% consent withdrawals after booster vaccination. This highlights the distinction between consent declines in vaccine studies in a pandemic versus an epidemic setting.

The COVID-19 RCT with the highest consent decline rate (16%) was the use of Hydrocortisone as treatment for severe COVID-19 hospitalized patients. This was a multi-centric RCT in several countries where one arm was local standard of care which did not include hydrocortisone. This potentially could have accounted for the higher consent decline rate seen. Another RCT had a 5% consent decline rate and this was the use of HCQ as post-exposure prophylaxis among participants who had either household or occupational exposure to a confirmed COVID-19 person. This is only slightly higher than the average consent decline rate of 4.3% and could be due to the fact that the efficacy of HCQ was frequently questioned both in scientific literature and the lay press.

The present study showed a lower consent withdrawal rate in standard of care/best supportive care arm than in interventional arm in COVID-19 RCTs. One amongst few reasons for this may have been participant’s refusal for diagnostic tests and investigations in the interventional arm which needed to be done multiple times. The uncertainty or psychological distress surrounding the pandemic could also have led to participant’s withdrawal from the study.

Our study has several limitations. First, it has focused only on English language RCTs published in PubMed/Medline. Secondly, a large number of COVID-19 and non-COVID-19 RCTs that did not satisfy the selection criteria were excluded. Third, whether the participant themselves or their LARs declined or withdrew consent is a surmise but the data is not given in the publications. Fourthly, we did not have data on consent withdrawals in the historical controls and hence the comparison was not done. Finally, the data on impact of co-variates such as economic status of the country and age of patients on consent declines and consent withdrawals was not available.

In summary, the present study shows a significantly lower rate of consent declines in COVID-19 RCTs relative to non-COVID-19 RCTs during a pandemic setting. The findings were also similar for RCTs conducted in a pandemic setting when compared with a non-pandemic setting. The physicians who undertake studies should spend more time on the
informed consent process to prevent or minimize therapeutic misconceptions during the pandemic so as to ensure adequate participant understanding and comprehension.

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Conflicts of interest
There are no conflicts of interest.

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