Inhaled budesonide in the treatment of early COVID-19 illness: a randomised controlled trial

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Abstract

Background

Multiple early hospital cohorts of coronavirus disease 2019 (COVID-19) showed that patients with chronic respiratory disease were significantly under-represented. We hypothesised that the widespread use of inhaled glucocorticoids was responsible for this finding and tested if inhaled glucorticoids would be an effective treatment for early COVID-19 illness.

Methods

We conducted a randomised, open label trial of inhaled budesonide, compared to usual care, in adults within 7 days of the onset of mild Covid-19 symptoms. The primary end point was COVID-19-related urgent care visit, emergency department assessment or hospitalisation. The trial was stopped early after independent statistical review concluded that study outcome would not change with further participant enrolment.

Results

146 patients underwent randomisation. For the per protocol population (n=139), the primary outcome occurred in 10 participants and 1 participant in the usual care and budesonide arms respectively (difference in proportions 0.131, 95% CI (0.043 to 0.218), p=0.004). The number needed to treat with inhaled budesonide to reduce COVID-19 deterioration was 8. Clinical recovery was 1 day shorter in the budesonide arm compared to the usual care arm (median of 7 days versus 8 days respectively, logrank test p=0.007). Proportion of days with a fever and proportion of participants with at least 1 day of fever was significantly lower in the budesonide arm. Fewer participants randomised to budesonide had persistent symptoms at day 14 and day 28 compared to participants receiving usual care. Budesonide was safe with only 5 (7%) of participants reporting self-limiting adverse events.

Conclusion

Early administration of inhaled budesonide reduced the likelihood of needing urgent medical care and reduced time to recovery following early COVID-19 infection.
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Research in context

Evidence before this study

The majority of interventions studied for the COVID-19 pandemic are focused on hospitalised patients. Widely available and broadly relevant interventions for mild COVID-19 are urgently needed.

Added value of this study

In this open label randomised controlled trial, inhaled budesonide, when given to adults with early COVID-19 illness, reduces the likelihood of requiring urgent care, emergency department consultation or hospitalisation. There was also a quicker resolution of fever, a known poor prognostic marker in COVID-19 and a faster self-reported and questionnaire reported symptom resolution. There were fewer participants with persistent COVID-19 symptoms at 14 and 28 days after budesonide therapy compared to usual care.

Implications of all the available evidence

The STOIC trial potentially provides the first easily accessible effective intervention in early COVID-19. By assessing health care resource utilisation, the study provides an exciting option to help with the worldwide pressure on health care systems due to the COVID-19 pandemic. Data from this study also suggests a potentially effective treatment to prevent the long term morbidity from persistent COVID-19 symptoms.

Introduction

COVID-19 is the most serious pandemic for over 100 years and with increasing mortality and morbidity worldwide. Other than age, obesity, and gender[1,2], there are no clear predictors to forecast who will deteriorate needing hospital-based care. The onset of COVID-19 illness is almost always mild[3] giving a potential window to intervene prior to the development of severe disease[1,2].To date, the majority of studies have focussed on investigating and treating severe and hospitalized COVID-19 infection[4]. However, there is currently little knowledge on therapeutic targets in early COVID-19 infection to prevent progression and clinical deterioration, although investigation with targets such as monoclonal antibodies are being studied[5].

In early reports describing COVID-19 infection from China[1,2], Italy[6] and the United States[7], there was a significant under representation of patients with asthma and chronic obstructive pulmonary disease (COPD) in patients hospitalized with COVID-19. We hypothesized that this may be due to the widespread use of inhaled glucocorticoids in these patients[8]. Furthermore, the main indication for the use of inhaled glucocorticoids in patients with asthma and COPD is to reduce exacerbations, which are recognized to be often viral in etiology[9]. In-vitro studies have shown that inhaled glucocorticoids reduce the replication of SARS-CoV-2 in airway epithelial cells[10] in addition to the downregulation of expression of angiotensin converting enzyme-2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) genes which are critical for viral cell entry[11].

Here we present the analysis of the Steroids in COVID-19 (STOIC) trial, a phase 2 trial designed to evaluate the efficacy of a widely used inhaled glucocorticoid budesonide in individuals with early COVID-19 disease in the community. We examined the effect of inhaled budesonide on likelihood of urgent care or hospitalization, clinical recovery and parameters of physiology such as temperature and oxygenation. We also evaluated the effect of inhaled budesonide on SARS-CoV-2 viral load.

Methods

Trial Design

The STOIC trial is a randomised, open-label, parallel group phase 2 clinical trial conducted in the community in Oxfordshire, United Kingdom. Adults over the age of 18, with symptoms suggestive of COVID-19 (new onset cough, fever and/or anosmia) within 7 days were eligible for inclusion. Participants were excluded if they had recent use (within 7 days) of inhaled or systemic glucocorticoids or if there was a known allergy or contraindication to inhaled budesonide. Recruitment for the study was via local primary care networks, local COVID-19 testing sites and via multi-channel advertising. Volunteers were able to contact the study staff using the advertised phone numbers or via e-mail and all participant information was publicly available on the study website (www.stoic.ndm.ox.ac.uk). The trial was registered on clinicaltrials.gov (NCT04416399).

Study intervention and assessments

Participants who met the inclusion criteria were randomised to usual care (UC) or intervention with budesonide (BUD) dry powder inhaler (Pulmicort Turbuhaler, AstraZeneca) at a dose of 800µg (2 puffs) twice a day. In the U.K., UC was supportive therapy with National Health Service (NHS) advising patients with COVID-19 symptoms to take anti-pyretics for symptoms of fever (products containing paracetamol, or non-steroidal anti-inflammatories such as aspirin and ibuprofen) and honey for symptoms of cough. Participants were seen at their homes at randomisation (day 0), day 7 and day 14 by a trained respiratory research nurse to obtain written informed consent, provide inhalers and to obtain (self-performed) nasopharyngeal swabs for SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) testing (see **supplementary methods** for further details)**.** Each participant received a paper symptom diary, calibrated pulse oximeter and thermometer for daily home monitoring. All participants were telephone contacted daily to record oxygen saturations, temperature and assessed for any adverse events by the study team. Participants allocated BUD were asked to stop taking the inhaler when they felt they had recovered (self-reported symptom recovery) or if they hit primary outcome; and all participants ceased daily monitoring (including daily telephone calls) when symptoms had recovered (self-reported symptom recovery) or if the primary outcome was achieved. Finally, at day 28, all study participants were seen in the trial centre and serum SARS-CoV-2 antibody testing was performed.

Outcomes

The primary outcome was defined as COVID-19-related Urgent Care visits including Emergency Department assessment or hospitalization. During the pandemic, members of the public in the United Kingdom were encouraged to contact a government telephone advice line prior to attending the emergency department and COVID-19 specific general practice hubs were created for patients who were deteriorating at home, for medical treatment including transfer to hospital. Secondary outcomes included clinical recovery as defined by self-reported time to symptom resolution; viral symptoms measured by the Common Cold Questionnaire (CCQ)[12] and the InFLUenza Patient-Reported Outcome (FLUPro®)[13] questionnaire; blood oxygen saturations and body temperature; and SARS-CoV-2 viral load.

Randomisation

Participants were randomly allocated to UC or BUD, stratified for participant age,(≤40 years/ >40 years) gender, and number of co-morbidities (≤1/ ≥2). The randomisation sequence was created using a random number generation function and allocation to each arm was performed through block randomisation in a 1:1 ratio.

Statistical Analysis

The statistical packages R (R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/), Gauss ((https://www.aptech.com/), and SAS v9.4 (https://www.sas.com/en_us/home.html) were used. Descriptive statistics were used to describe variables between the groups in the BUD arm and the UC arm. Appropriate parametric or non-parametric statistical tests were performed. For continuous variables, the difference between treatments in the means or medians and the corresponding 95% confidence interval were reported. For continuous variables, fixed-factor ANCOVA models (t-tests) adjusted for treatment, age group (> or <=40 years), sex, no. of comorbidities (<=1, >=2) and baseline or Wilcoxon rank sum tests were applied to compare the BUD and UC arm. For categorical variables the number (and percentage) of patients in each category were reported for each treatment group and chi-squared tests were used for comparing treatment arms. Confidence intervals for the difference in proportion was by normal approximation (Wald). Time to self-reported clinical recovery and FLUPro® symptom recovery were analysed using the Kaplan Meier method and presented as the median time to event with 95% confidence limits. Comparison were performed with a log rank test where participants with primary outcome were censored at Day 28 when not meeting the event. Sensitivity analysis for participants with confirmed COVID-19 infection was also performed for the primary outcome. All tests were performed at a 5% 2-sided significance level and all comparative outcomes are presented as summary statistics with 95% confidence intervals and reported in accordance with the CONSORT Statement. Missing data from study visits and daily monitoring were handled by last observation carried forward (LOCF) for temperature, oxygen saturations and time to FLUPro® symptom resolution. For FLUPro® total score and individual domain time-series plots, missing data was handled by LOCF or imputation of zero score when self-reported symptom resolution. Less than 1% of data was determined as missing. Stochastic simulations of a "virtual" trial with the same study design, primary endpoint and duration, and community detection are presented in full in the **supplementary materials.** P-values are reported to a maximum of 3 decimal places. Further full details are available in the **supplementary material**.

Sample size estimation

At study inception in March 2020 and using published data available at the time[1,2], we assumed that 20% of all COVID-19 illness is severe and would require hospitalisation. Using 80% power at 0.05 level, we required 199 patients in each arm to demonstrate a 50% reduction of urgent care visits or hospitalizations. The primary outcome was analysed for both the per-protocol (PP) and intention to treat (ITT) population. The PP population is defined as the population that received the study treatment and had at least 1 day of study observations; the ITT population is defined as all participants that were randomized to a study arm.

Institutional Review

The trial was sponsored by the University of Oxford, and was approved by the Fulham London Research Ethics Committee (20/HRA/2531) and the National Health Research Authority. The BUD was open label. All participants provided written informed consent. The study team requested an independent statistical monitoring committee review on the 9th of December 2020 due to reduced recruitment after the second national lockdown in England; implementation of the COVID-19 vaccine; and ethical consideration of the primary outcome. *A priori* stop criteria were used to determine futility of further recruitment (**see statistical analysis plan**).

Role of funder

The study was funded by the Oxford NIHR Biomedical Research Centre and AstraZeneca (Gothenburg, Sweden). The funders had no role in study design, data collection, data analysis, data interpretation, writing nor the decision to publish. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Results

Participants

From the 16th July to the 9th December 2020, 146 participants were randomised, of which 139 were in the PP analysis, with 70 and 69 in the BUD and UC arm respectively (**see figure 1).** Participant characteristics were similar between the study arms, as shown in **table 1** (see **supplementary table 1 for ITT population**). SARS-CoV-2 infection was detected in 137 participants (94%) measured by RT-PCR. Serological conversion was detected in 55% (67/122 samples). The median (IQR) duration of symptoms prior to randomisation was 3 (2 to 4) days. The median (IQR) time to symptom resolution was 7 (5 to 11) days. BUD was taken for a median (IQR) duration of 7 (4 to 10) days.

Conditional power

Simulations using bootstrap was performed to determine the conditional power for an evaluation of an early stop, using the *a priori* decisions described in the supplement. Estimated power was >99% using both the total population (N=124) and, at the time of the simulation, sensitivity analysis for the known subgroup of SARS-CoV-2 positive patients (N=78).

Primary outcome

For the ITT population, the primary outcome occurred in 11 (15%) participants in the UC arm and 2 (3%) participants in the BUD arm (difference in proportion 0.123, 95%CI (0.033 to 0.213), p=0.009). In the PP analysis, the primary outcome occurred in 10 participants (14%) in the UC arm versus 1 participant (1%) in BUD arm (difference in proportions 0.131, 95% CI (0.043 to 0.218), p=0.004) indicating a relative risk reduction of 91% for BUD. The number needed to treat with inhaled budesonide to reduce COVID-19 related urgent care/hospitalization was 8. Sensitivity analysis in participants with confirmed COVID-19, 8 (14.1%) vs 1 (1.5%), showed that the difference in proportions was 0.125, 95% CI (0.035 to 0.216), p=0.007. There was no difference in participants with a primary outcome event compared to those without (**see supplementary table 2**). For all primary outcome events, 3 participants were symptomatically breathless with oxygen saturations below 94%; 1 developed diabetic ketoacidosis; 1 developed acute kidney injury; 1 had suspected pulmonary embolism; 1 had suspected rib fractures; 3 were seen at least twice by an out of hours general practitioner (which included the 1 participant in the BUD arm); and 1 was seen by a paramedic crew on day 6 and subsequently seen again by a general practictioner on day 8 and sent to ED, where they were directly admitted to the Respiratory High Dependency Unit requiring continuous positive pressure ventilation for 8 days. All participants not admitted to hospital had daily telephone checks with the COVID Hub general practicitioner team.

Secondary outcomes

Self-reported clinical recovery was 1 day quicker with BUD compared to UC (median, 95%CI of 7 (6 to 9) days versus 8 (7 to 11) days, logrank test p=0.007, **see figure 2**). The mean (SD) time to recovery, in days was 8 (5) and 12 (8) in the BUD and UC arm respectively. Further sensitivity analysis for clinical recovery in participants with confirmed SARS-CoV-2 showed a similar median (95%CI) times to recovery (7 (6 to 9) vs. 8 (7 to 10) days, p=0.012) **(see supplementary figure 1).** At day 14, self-reported symptoms were present in 10% (n=7) of participants randomised to BUD compared to 30% (n=21) randomised to UC (difference in proportion 0.204, 95%CI (0.075 to 0.334), p=0.003).

The mean proportion of days with a documented fever (≥37.5 C) during the first 14 days, was 2% (SD 6%) in the BUD and 8% (SD 18%) in the UC arms (Wilcoxon test, p= 0.051; Hodge-

Lehmann median 0% (95% CI 0, 0)). The percentage of participants with at least 1 day of fever was 11% (n=8) and 23% (n=16) in the BUD and UC arm respectively (difference in proportion 0.067, 95% CI (-0.678, 0.242), p=0.076). Violin plots, showing the distribution of pooled highest temperatures are presented in **figure 3,** demonstrating a statistically higher mean in the UC arm (mean difference 0.49, 95%CI 0.32 to 0.66, p<0.001). Temperature plots relative to the day of randomization showed that temperature fell quicker in the BUD compared to UC arm **(see supplementary figure 2)**. The median (IQR) proportion of total days that participants required as-needed antipyretics (paracetamol, aspirin, ibuprofen) in the BUD and UC arms was 27% (0 - 50) and 50% (15 - 71) respectively (Wilcoxon test, p=0.025).

Symptom resolution at day 14, as defined by the FLUPro® user manual, occurred in 82% (n=55) and 72% (n=49) of the BUD and UC arms respectively (difference in proportions 0.100, 95% CI (-0.040, 0.241), p=0.166); whilst the median (95%CI) time to symptom resolution as measured by the FLUPro® was 3 (2 to 5) and 4 (3 to 6) days in the BUD and UC arms respectively (logrank test p=0.080, **see supplementary figure 3**). The mean change (95%CI) in FLUPro® total score between day 0 and day 14 in the BUD and UC are -0.65 (-0.80 to -0.50) and -0,54 (-0.69 to -0.40) respectively (mean difference of -0.10, 95%CI of the difference -0.21 to -0.00, p=0.044). **Figure 4 (panels a-g**) shows the mean daily FLUPro® scores for the total symptom burden and individual domains. The mean change of the FLUPro® domains showed that systemic symptoms were significantly greater in BUD compared to UC (**supplementary table 3).** The mean (95%CI) change in CCQ total score between day 0 and day 14 in the BUD and UC was -0.49 (-0.63 to -0.35) and -0.37 (-0.51 to -0.24) respectively (mean difference of -0.12 (-0.21 to -0.02), p=0.016). The CCQ symptom daily mean score is presented as **supplementary figure 4**.

The proportion of days with oxygen saturations ≤94%, during the first 14 days, was 19% (SD 24%) and 22% (SD 27%) in the BUD and UC arm respectively (Wilcoxon test p=0.627; Hodge-Lehmann median 0 (95% CI (-0.07, 0)). During the first 14 days 59% (n=41) and 58% (n=40) in the BUD and UC arms had at least one day with oxygen saturations ≤94% (difference in proportions 0.006, 95% CI (-0.158, 0.170), p=0.943).

The median (IQR) cycle threshold (CT) nasopharyngeal SARS-CoV-2 viral load at Day 0, day 7 and day 14 was 32.1 (21.7 - 40.0), 35.3 (32.4 - 40.0) and 36.4 (34.2 - 40.0) respectively. There was a significant difference in CT reduction between visit 1 and 2 for both study arms (Wilcoxon matched pairs P=0.063 (BUD) and 0.004 (UC), **see supplementary figure 5**); but no difference in reduction between groups (mean (95% CI) change between visit 1 and 2 in the BUD and UC was 3.20 (0.46 to 5.94) and 3.75 (1.00 to 6.50) respectively (mean difference of -0.55 (95% CI -2.39, 1.29) p=0.554).

The safety profile of BUD was as expected, with an adverse event reported in 5 participants (4 had sore throat; 1 had dizziness). Each of these were all self-limiting and fully resolved on cessation of BUD.

Further analysis

Stochastic simulations, in a 'virtual twin' post-hoc study design, demonstrated that the daily odds ratio of reaching the primary outcome, with BUD reduced by 3000% (**see figure 5** and **supplementary materials)**.

Discussion

We have demonstrated that the inhaled glucocorticoid, budesonide, given for a short duration, may be an effective treatment of early COVID-19 disease in adults. This effect, with a relative reduction of 91% of clinical deterioration is equivalent to the efficacy seen following the use of COVID-19 vaccines[14] and greater than that reported in any treatments used in hospitalised and severe COVID-19 patients[15]. Our study demonstrated a 14% incidence of urgent healthcare need and is consistent with other community based studies[16]. Our findings indicate that the primary outcome events were not mild events, despite occurring in participants with a mean age of 45 years with a spectrum of COVID-19 complications from deterioration of a pre-morbid condition (diabetic ketoacidosis), to the need for prolonged respiratory support. Although, there is an indication to target the population at risk of severe illness, such as the older and frailer patient with SARS-CoV-2 infection, the real world setting shows that the majority of the population that will get COVID-19 are not old and only 9% of the global population are over the age of 65 years[17]. Moreover, it would be unethical to ignore symptoms and to omit treatment for a younger person who has a lower population risk of severe COVID-19. During the study, the local management approach of COVID-19 changed to directing patients to COVID-19 hubs as a substitute to ED attendance. Despite this, we could see that the majority of the primary outcome events required hospital assessment.

The broad inclusion criteria make this study intervention relevant to health care systems worldwide. Inhaled budesonide is a simple, safe, well studied, inexpensive and widely available treatment. The number of participants needed to treat to prevent increased health care resource utilization is 8, and combined with the short treatment period required to achieve benefit, makes this potentially an affordable and scalable intervention for early COVID-19. This is especially significant in low- and middle-income countries where the majority of currently approved COVID-19 treatments are unlikely to ever reach patients as a consequence of variable healthcare systems[18]. For example, although dexamethasone is a widely available and cheap medicine, with efficacy in reducing mortality in severe and intensive care related COVID-19[19], and the potential for monoclonal antibody targets in early COVID-19[5], this is unfortunately irrelevant in countries which have limited intensive care, hospital capacity or functioning healthcare systems[20]. Furthermore, in high income countries, inhaled budesonide could work as an adjunct to reduce pressure on health care systems until widespread SARS-CoV-2 vaccination can be achieved. Additionally, the efficacy of inhaled budesonide is unlikely to be affected by any emergent SARS-CoV-2 variant which have been a source of concern with vaccine implementation[21].

We selected this treatment intervention due to the unexpected observation of an under-representation of patients with asthma and COPD with severe COVID-19[22]. This finding from early hospitalised cohorts in Wuhan[1,2] was at odds with prior respiratory viral pandemics, such as H1N1 influenza[23]. The common therapy between these lung diseases is inhaled glucocorticoids, either as a mono-, dual- or triple- constituent. Furthermore, inhaled glucocorticoids are among the most prescribed medicine of any class around the world, listed by the World Health Organisation (WHO) of essential medicines. Moreover, evidence of the utility of inhaled glucocorticoids, in reducing viral exacerbations of asthma have been known for many decades[24], whilst specifically, inhaled budesonide has shown effect at reducing rhinovirus replication *in-vitro*[25]. Furthermore, single maintanence and reliever therapy has previously been shown to reduce asthma hospitalizations following influenza or the common cold (frequently a coronavirus)[9]; whilst recent reports in asthmatics with SARS-CoV-2 infection have repeatedly shown protective effects[26-28]. The efficacy of dexamethasone in RECOVERY[19], for severe disease also supports our findings, whilst there is plausibility that

the immune-modulatory effect of inhaled glucocorticoids, may also apply to any future viral epidemics, but require further evaluation.

In our study, we found that inhaled budesonide also demonstrated benefit in the secondary outcomes, with quicker symptom resolution in those treated with budesonide either measured using a self-report of symptom recovery, or defined as normalisation of prospectively collected symptom scores measured using the FluPRO®[13] or the CCQ[12]. Of note, there was a significantly greater population of participants randomised to budesonide who were free of symptoms at 28 days compared to participants randomized to usual care. In the face of the evolving nature of chronicity of symptoms following COVID-19 illness, our finding of an impact on both patient reported and patient measured symptoms are important[29]. In the United Kingdom, up to 20% of patients[30] report persistent symptoms 5 weeks after COVID-19. Our findings thus also suggests that intervention with an inhaled glucocorticoid might impact on rate of the persistent long-term symptoms in COVID-19 ("long COVID"); and should be investigated further in view of the significant long-term health and economic impact of long COVID. Excitingly, there are several open-label studies currently open to recruitment examining the role of inhaled budesonide in COVID-19 infection (ISRCTN86534580, NCT04355637, NCT04331054) and others investigating the role of inhaled ciclesonide (NCT04330586, NCT04377711, NCT04381364, NCT04356495); whether these studies also demonstrate an impact on long COVID will be of importance

The positive impact on temperature when used to treat early COVID-19 is further evidence that inhaled budesonide is modifying the disease process. Fever has been repeatedly shown to be a poor prognostic marker in severe COVID-19 illness[1,2] and our findings that budesonide signficiantly reduces this by clinical measurement and by anti-pyretic use as a surrogate is further supportive that this therapy is likely to be an effective treatment for COVID-19.

Our study examined the effect on viral titres as a secondary outcome and showed no difference between intervention groups. We were unable to demonstrate a mechanistic significant difference in reduction in viral load between budesonide and usual care, as per previous in-vitro data[10]. Our study returned lower viral copies (as measured by cycle threshold) compared to other studies[31], but this is expected in view of the fact that swabs were self-taken, where we expect the viral yield to be lower. Moreover, assay sensitivity for detection of SARS-CoV-2 is recognised to be variable[32] and further comparisons taking into consideration the natural decay of virus in the nasopharynx to compare against an intervention are warranted.

Limitations

Our study design involved randomisation at home, with home visits for study assessments and a daily contact until symptom resolution by the study team which limited participant drop-outs and enhanced the completion of symptom diaries. However, there are limitations to our study. Firstly, this is an open-label study, performed out of expediency, where a placebo controlled arm was not practical at the time of study inception. In comparison to the awaited randomised clinical trials investigating the efficacy of inhaled glucocorticoids (described above), with the exception of one (NCT04377711) all are open-label and not placebo controlled and thus consistent with our study design. Although there is concern with respect to introducing bias, the expected degree of real bias in an open-label study for a new disease is unknown. Secondly, the study was stopped early due to the impact of the national pandemic control measures, with a second national lockdown, and national prioritisation rules for clinical research trials in the UK, which prevented recruitment from outside the local region. Thirdly, our study did not reach the sample size. Our power calculations were made from the best available predictions in early 2020. Therapeutic randomised clinical trial design and sample size calculations are often dictated by statistical assumptions with treatment effect estimations

based on the evidence of best available care. However, in trial design for a new disease, with no known effective treatment, statistical assumptions are thus arbitrary. We found that the budesonide treatment effect size, was larger than predicted; and independent statistical simulations concluded that the final sample size and treatment effect had a 99% power to reject the null hypothesis. In addition to this, the post-hoc stochastic simulations also provided estimations that the effect size could be construed as real; whilst the positive concordance of temperature and symptoms as secondary outcomes gives us confidence in our results. These aspects were crucial aspects to assess the validity of the study. Our inclusion criteria were very general and our study population is younger, with fewer comorbidities than patients that are known to have increased mortality[2]. However, as discussed earlier, our population reflects the general global population, in whom we found a 1 in 7 risk of harm from COVID-19, but with minor self-limiting side effects of inhaled budesonide. Finally, stopping a study early is unusual and is a decision which is not taken without due diligence[33]. However, we ensured that *a priori* stop decision analysis was performed by an independent statistical team for statistical rigor.

Conclusion

In conclusion, budesonide, an inhaled glucocorticoid, appears to be an effective treatment for early COVID-19 infection which could be applicable to global healthcare systems. Our findings require urgent validation and dissemination, especially in the setting of a treatment given early that is widely available and relatively safe.

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Author Contributions:

MB, SR, PJB, DVN, REKR contributed to the literature seach, study design, data interpretation, and the critical revision of the work. SR, DVN, BL, MM, HJ, CM, KK, RF, IB, VG, SB, CB, REKR, MB contributed to the recruitment of participants. SR, BL, HJ, CM, KK, MM performed all study assessments, study visits and completed data entry. MM, PCM, LED, JLS, PJB, JLC, JRB supported the laboratory assessments and RT-PCR. AH performed the block randomisation. TB and SP were the independent statisticians and analysed all data. DVN and NTF provided additional statistical support. TB, SP, DBN, NF, SR and MB have accessed and verified the data. All authors contributed to the writing of the manuscript and approved its submission. MB was responsible for the decision to submit the manuscript.

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Dr. Bafadhel reports grants from AstraZeneca, personal fees from AstraZeneca, Chiesi, GSK, other from Albus Health, ProAxsis, outside the submitted work;

Data Sharing Statement

De-identified individual participant data and a data dictionary defining each field in the set, can be made available to others upon approval of a written request to the corresponding author. The request will be evaluated by a committee formed by a subset of co-authors to determine the research value. A data sharing agreement will be needed.

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Table 1. Demographics and clinical characteristics of study participants in the per-protocol population at study enrollement.

Characteristic	**Budesonide (n = 70)**	**Usual care (n = 69)**
Age, years#	44 (19-71)	46 (19-79)
Female sex, no. (%)	39 (56%)	41 (59%)
White ethnicity, no. (%)	65 (93%)	64 (93%)
Body mass index, kg/m^2	27 (4.9)	26 (4.6)
Number of co-morbidities no.¥	1 (0-2)	1 (0-1)
Cardiovascular Disease, n (%)	6 (9%)	6 (9%)
Diabetes, n (%)	3 (4%)	4 (6%)
Past or current history of Asthma, n (%)	11 (16%)	10 (14%)
Duration of symptoms, days¥	3 (2-5)	3 (2-4)
Evidence of COVID positive status, no. (%)	66 (94%)	65 (94%)
Presence of symptoms at baseline, no. (%)		
Cough	55 (79%)	48 (70%)
Fever	49 (70%)	44 (64%)
Headache	40 (57%)	38 (55%)
Fatigue	32 (46%)	23 (33%)
Loss of sense of smell/taste	25 (36%)	30 (43%)
Gastrointestinal symptoms	11 (16%)	12 (17%)
Breathlessness	11 (16%)	11 (16%)
Myalgia	6 (9%)	10 (14%)
Nasal symptoms	3 (4%)	5 (7%)
Sore throat	0 (0%)	2 (3%)
Chest pain/tightness	4 (6%)	1 (1%)
Other	7 (10%)	8 (12%)
Highest temperature recorded*¥	36.6 (36.2- 37.1)	36.6 (35.5-38.3)
Lowest Oxygenation recorded as % saturation*¥	96 (95-97)	96 (95-97)
SARS-CoV-2 viral cycle threshold¥	32.6 (22.4-39.4)	31.8 (15.6-40.0)

Data presented as mean (SD) unless stated otherwise; #mean (range); *at randomisation; ¥median (IQR);

Figure legends

Figure 1. *Consort flow diagram*

Figure 2. *Time to self-reported clinical recovery of per protocol population using data censoring for primary outcome. BUD = budesonide; UC = usual care*

Figure 3*. Violin plots illustrating pooled peak (maximum) temperature in participants in BUD and UC arms, with statistically significant difference in the mean temperature (mean difference 0.49, 95%CI 0.32-0.66, p<0.001). BUD = budesonide; UC = usual care*

Figure 4*. Daily mean scores over 14 days using the FLUPro® questionnaire. Panel (a) total symptoms; (b) systemic symtoms (c) nasal symptoms; (d) throat; (e) chest; (f) eyes; (g) gastrointestinal. BUD = budesonide; UC = usual care. Vertical bars indicate standard error.*

Figure 5*. Relationship between treatment effect, here defined as the daily ratio of the odds of reaching primary outcome (PO) in the UC vs BUD arms (horizontal axis) and the ratio of primary event outcomes in the UC vs BUD arms at the completion of the trial (vertical axis). Plots derived from numerical simulations of the stochastic "virtual twin" trial. These indicate that in order to observe our findings (shown by the dotted line), then the daily treatment effect needed represents approximately 3000% (30x) reduction in the daily odds of reaching primary outcome.*

Figure 1

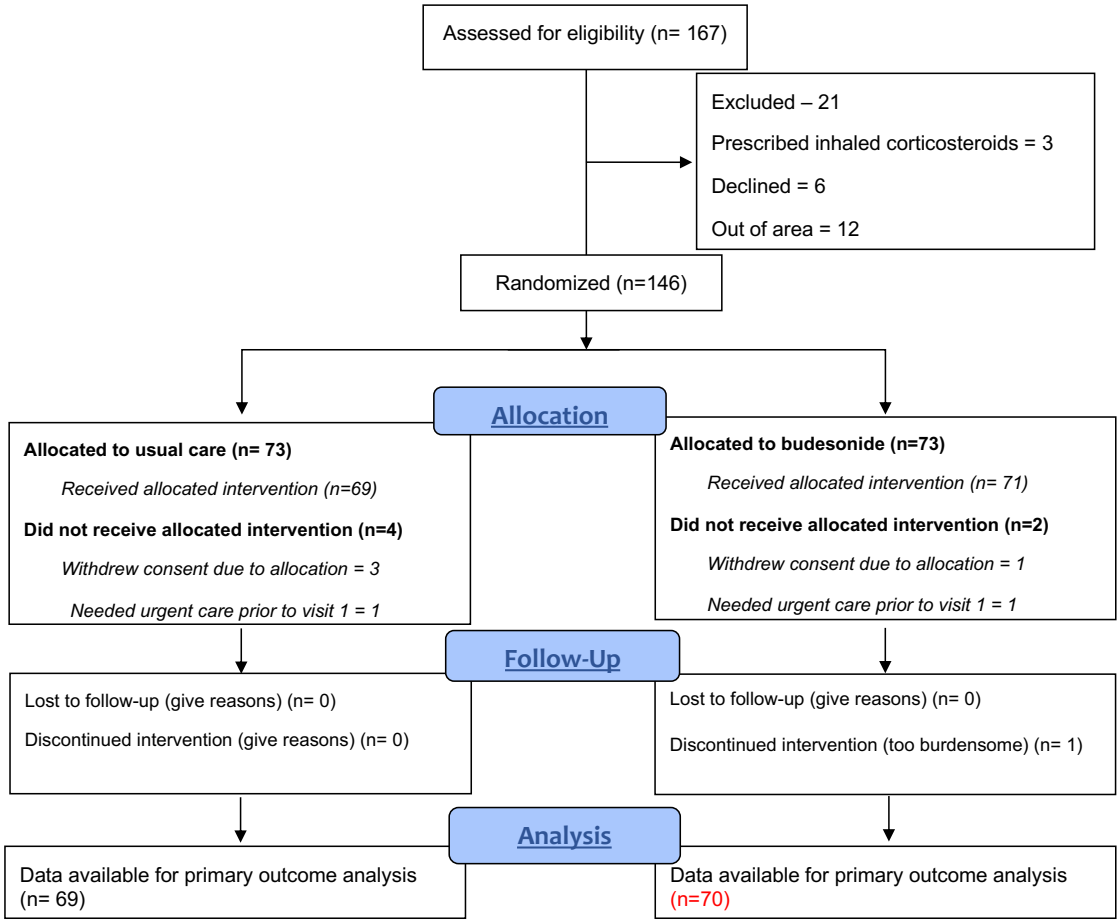

Assessed for eligibility (n= 167)
Excluded – 21
Prescribed inhaled corticosteroids = 3
Declined = 6
Out of area = 12
Randomized (n=146)
Allocation
Allocated to usual care (n= 73)
Received allocated intervention (n=69)
Did not receive allocated intervention (n=4)
Withdrew consent due to allocation = 3
Needed urgent care prior to visit 1 = 1
Allocated to budesonide (n=73)
Received allocated intervention (n= 71)
Did not receive allocated intervention (n=2)
Withdrew consent due to allocation = 1
Needed urgent care prior to visit 1 = 1
Follow-Up
Lost to follow-up (give reasons) (n= 0)
Discontinued intervention (give reasons) (n= 0)
Lost to follow-up (give reasons) (n= 0)
Discontinued intervention (too burdensome) (n= 1)
Analysis
Data available for primary outcome analysis (n= 69)
Data available for primary outcome analysis (n=70)

Figure 2

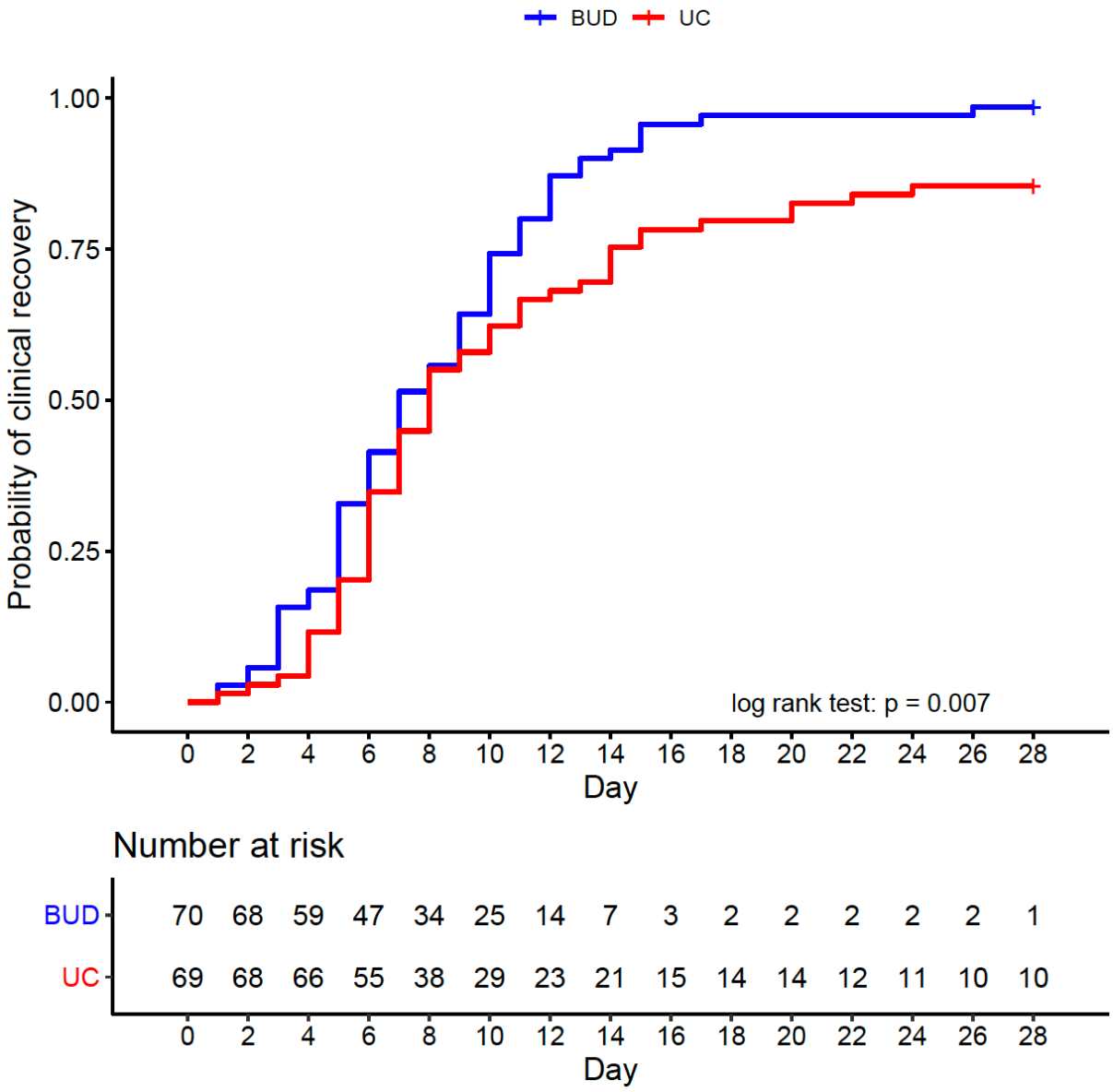

BUD
UC
Probability of clinical recovery
1.00
0.75
0.50
0.25
0.00
log rank test: p = 0.007
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
Day
Number at risk
BUD 70 68 59 47 34 25 14 7 3 2 2 2 2 2 1
UC 69 68 66 55 38 29 23 21 15 14 14 12 11 10 10
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
Day

Figure 3

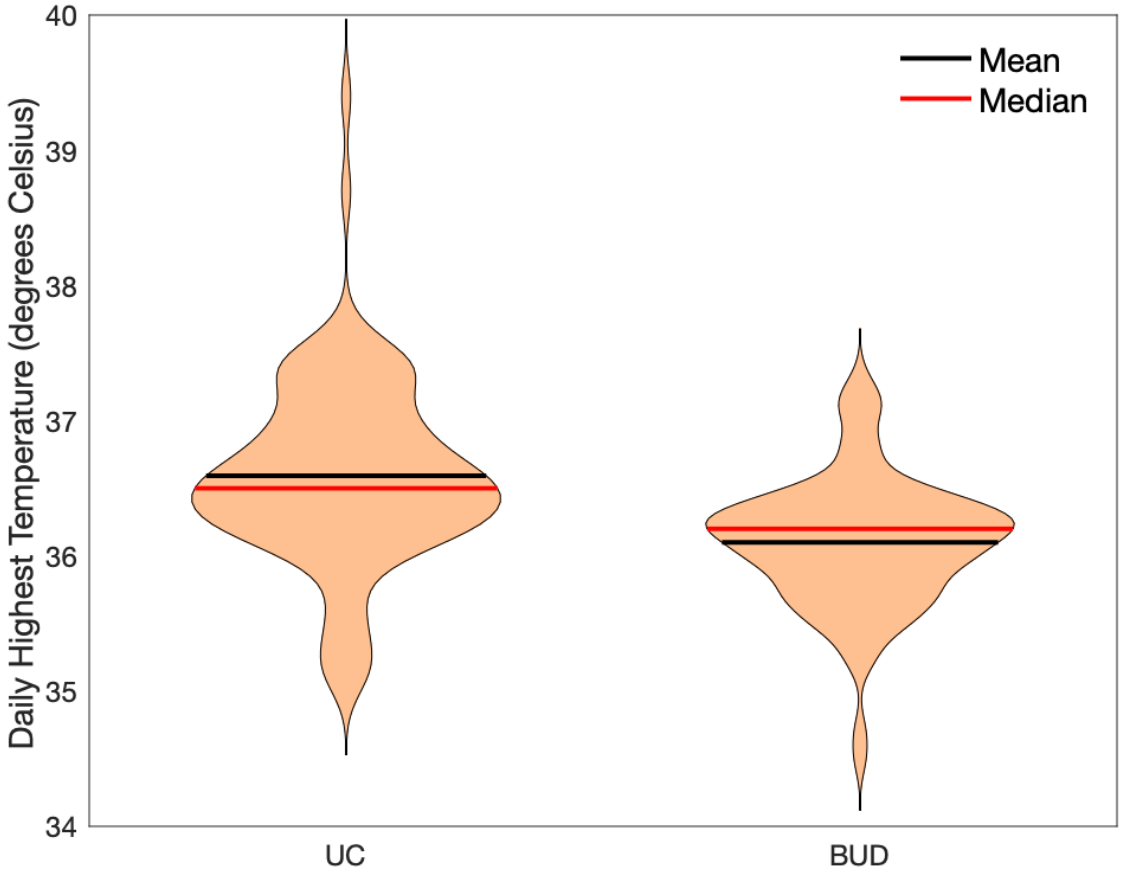
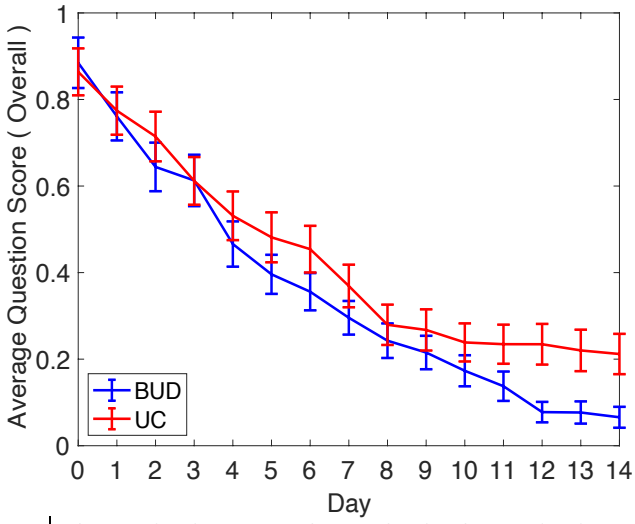
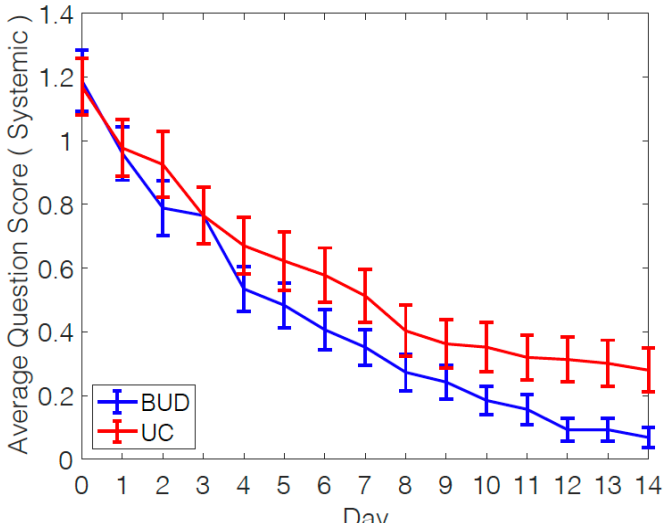

Mean
Median
Daily Highest Temperature (degrees Celsius)
40
39
38
37
36
35
34
UC
BUD

Figure 4 a



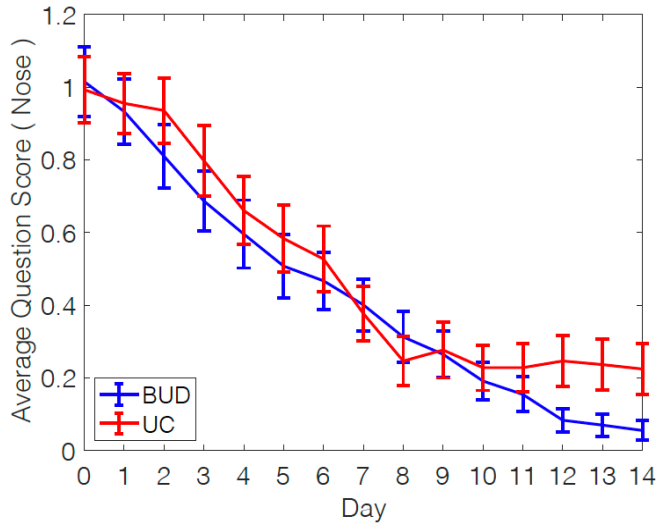
Day	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
N (BUD)	67	66	67	66	67	66	68	67	68	68	68	68	66	67	68
N (UC)	67	66	66	63	66	66	65	66	67	66	68	68	68	66	68

Figure 4b



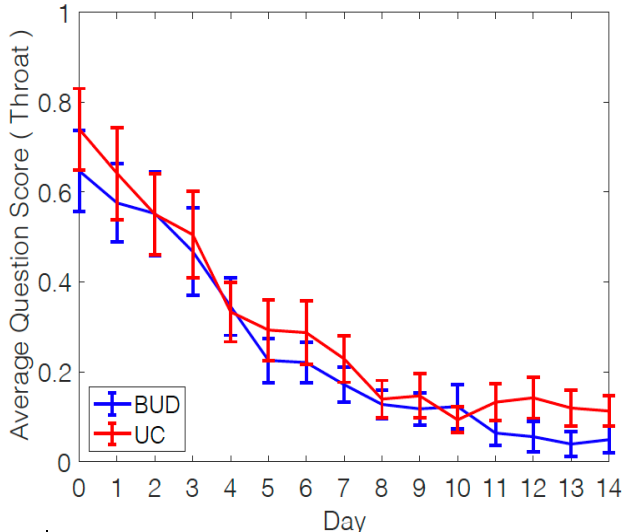
Day	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
N (BUD)	68	67	67	66	67	67	68	67	68	68	68	68	66	67	68
N (UC)	68	67	66	64	67	66	65	67	67	66	68	68	68	67	68

Figure 4c



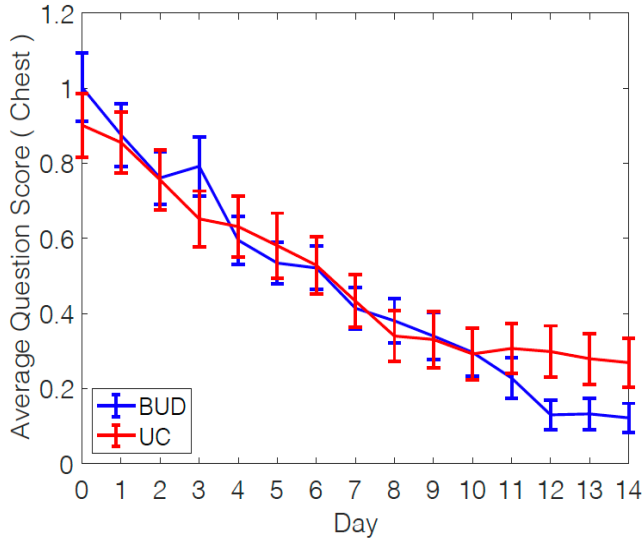
Day	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
N (BUD)	67	67	67	67	68	68	68	68	68	68	68	68	66	68	68
N (UC)	68	67	66	63	67	66	65	67	67	66	68	68	68	67	68

Figure 4d



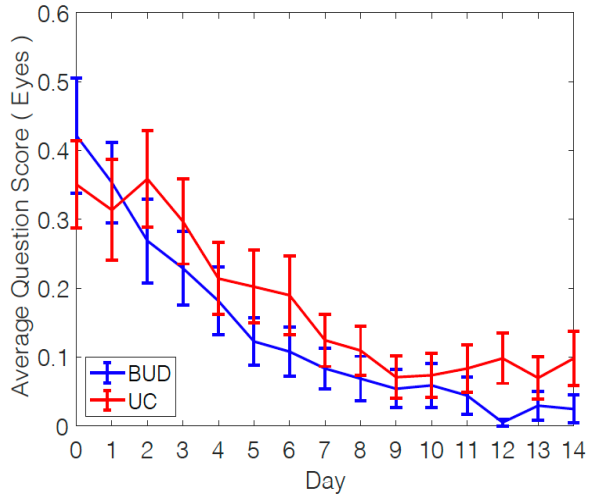
Day	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
N (BUD)	68	66	67	67	68	68	68	68	68	68	68	68	66	68	68
N (UC)	68	66	66	64	67	66	65	67	67	66	68	68	68	67	68

Figure 4e.



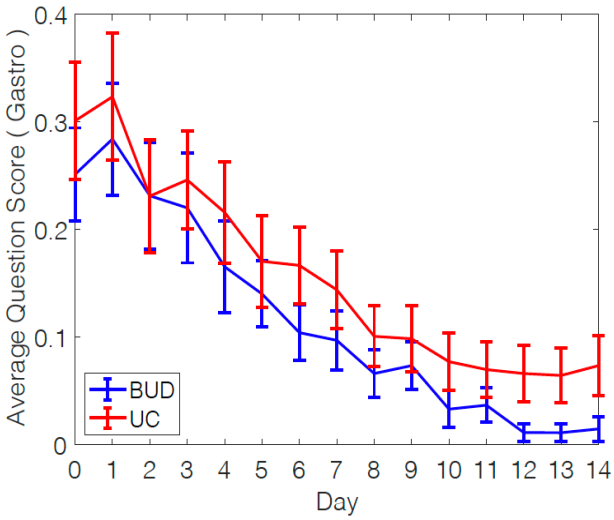
Day	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
N (BUD)	68	67	67	67	68	68	68	68	68	68	68	68	66	68	68
N (UC)	68	67	66	64	67	66	65	67	67	67	68	68	68	67	68

Figure 4f.



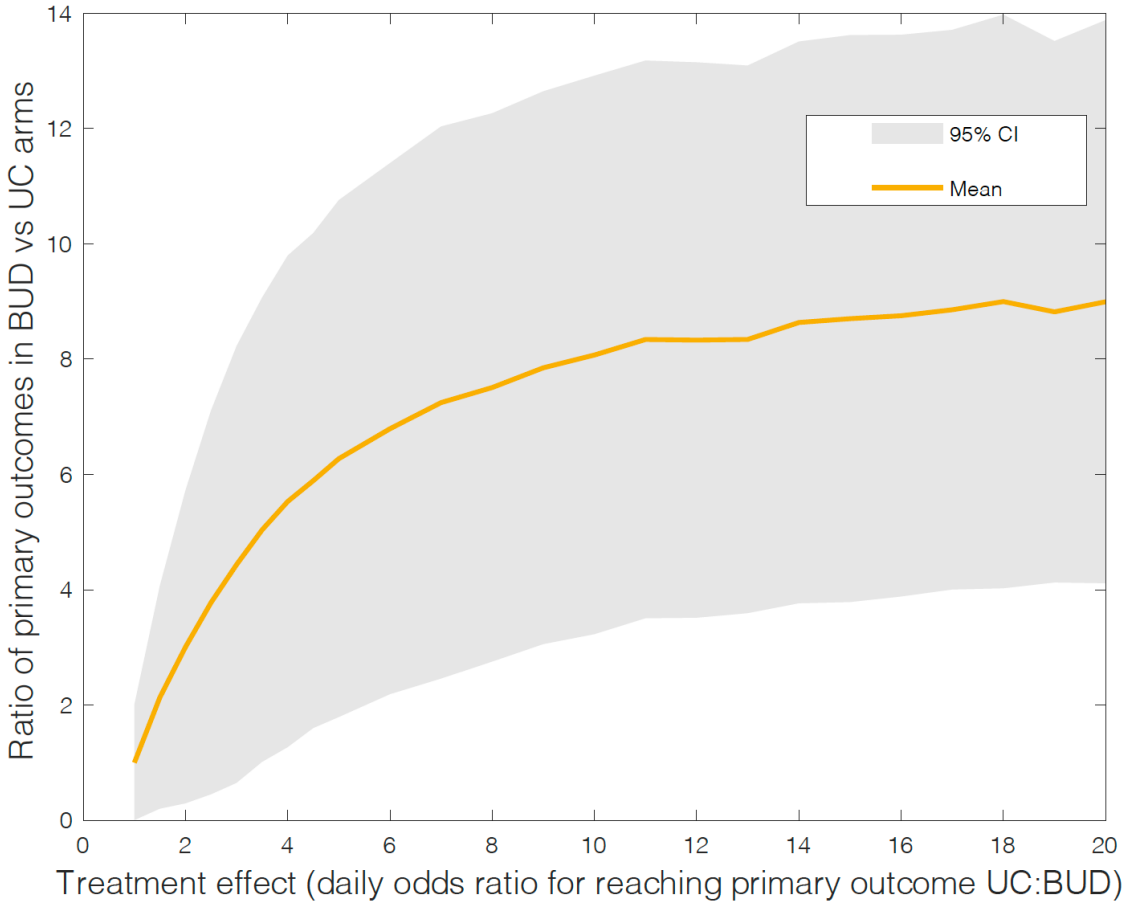
Day	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
N (BUD)	68	67	67	67	68	68	68	68	68	68	68	68	66	68	68
N (UC)	68	67	66	64	67	66	65	67	67	66	68	68	68	67	68

Figure 4g.



Day	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
N (BUD)	68	66	67	67	67	66	68	67	68	68	68	68	66	67	68
N (UC)	67	67	66	64	66	66	65	66	67	66	68	68	68	66	68

Figure 5


Ratio of primary outcomes in BUD vs UC arms
Treatment effect (daily odds ratio for reaching primary outcome UC:BUD)
95% CI
Mean
0
2
4
6
8
10
12
14
16
18
20