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Efficacy and safety of rivaroxaban, colchicine, and famotidine–loratadine with specialist supportive clinical care for fatigue in patients with post-COVID-19 condition in the UK: a multisite, open-label, randomised controlled trial

*STIMULATE-ICP consortium**

Summary

Background Post-acute sequelae of COVID-19 or post-COVID-19 condition (also known as long COVID) affects 1–5% of adults globally, most commonly with fatigue, and no evidence-based therapies are available. We aimed to evaluate the efficacy of repurposed medications in fatigue management in adults with long COVID.

Methods We did a phase 3, four-group, randomised, controlled, adaptive platform, open-label drug trial nested within a pragmatic, multicentre, cluster-randomised trial of an integrated care pathway (ICP) for long COVID across 12 UK National Health Service (NHS) specialist long COVID care clinics in the UK. Participants had to be adults (>18 years) with long COVID who had not been hospitalised with COVID-19. In addition to NHS specialist-led long COVID care (hereafter, usual care), participants in the ICP trial could receive multiorgan MRI and clinical decision support and/or app-based rehabilitation. Initially, participants in the ICP trial were invited to enrol in the drug trial, but slow recruitment to the drug trial led to establishment of additional drug-only trial sites. Participants enrolled at either ICP trial sites or drug-only trial sites were randomly assigned (1:1:1:1) to receive colchicine 500 µg twice daily, rivaroxaban 10 mg once daily, famotidine 40 mg with loratadine 10 mg once daily, or no drug for 12 weeks. All participants received usual care. Randomisation was done electronically in blocks (various block sizes) and stratified by site, birth sex, ICP trial group allocation, and being a new or previous patient of a drug-only site. The primary endpoint was 12-week fatigue, assessed with the Fatigue Assessment Scale (FAS; with scores ranging from 10 [no fatigue] to 50 [debilitating fatigue], and a >10% change considered clinically meaningful) among randomly assigned individuals who had available baseline and 12-week data, adjusting for baseline fatigue and clinically relevant covariates. Secondary endpoints included 24-week FAS. The nested drug trial is registered, ISRCTN10665760. The trial is complete.

Findings Of 6035 eligible participants, 778 (383 co-enrolled in the ICP trial and 395 directly enrolled in the drug trial) were randomly assigned between Aug 22, 2022, and Aug 7, 2024 to colchicine (n=192), famotidine–loratadine (n=193), rivaroxaban (n=197), or no drug (usual long COVID care only; n=196). The mean age of participants was 46 years (SD 12·4), 495 (64%) of 778 were female, and 91 (12%) were from a non-White ethnic group. Across all trial groups, there was severe baseline fatigue (mean FAS score 36·8 [SD 7·49]) and a clinically relevant mean FAS reduction of 4·3 points to 32·5 (SD 9·13) at 12 weeks. Adjusted analyses showed small, statistically significant FAS reductions in the colchicine (–1·49 points [95% CI –2·92 to –0·06], p=0·041) and famotidine–loratadine (–1·48 points [–2·88 to –0·08], p=0·038) groups, but not in the rivaroxaban group (–1·06 points [–2·47 to 0·35, p=0·139), compared with no study drug at 12 weeks. However, 24-week FAS scores, 12 weeks after drug cessation, were not significantly different between groups. Treatment was well tolerated, with ten serious adverse events (requiring hospitalisation but unrelated to trial drugs) reported in eight (1·0%) of the 778 participants, five of which were in three participants in the rivaroxaban group.

Interpretation In participants with long COVID, severe fatigue reduced in all study groups—including the no drug group—over 12 weeks, with small additional reductions in the colchicine and famotidine–loratadine groups compared with the no drug group. Modest effects on FAS were not sustained after drug withdrawal. Long-term long COVID symptom benefit is unlikely with these drugs alone. Future trials could investigate the use of these or other repurposed drugs in specific subgroups of patients with long COVID, combination therapies, and how care is delivered.

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*Full list of authors is in the appendix

Correspondence to:
Prof Amitava Banerjee, Institute of Health Informatics, University College London, London NW1 2DA, UK
ami.banerjee@ucl.ac.uk

See Online for appendix

Research in context

Evidence before this study

We searched MEDLINE, Embase, and medRxiv from Jan 1, 2020, to April 1, 2026 for randomised controlled trials comparing the effects of repurposed pharmacological agents on fatigue in people meeting a clinical definition of post-COVID condition or long COVID. We used the search terms ("long COVID" OR "PASC" OR "post-COVID syndrome") AND ("colchicine" OR "famotidine" OR "loratadine" OR "antihistamine" OR "rivaroxaban" OR "apixaban" OR "anticoagulation"). We identified three trials that tested at least one of these agents in people with clinical sequelae following SARS-CoV-2 infection. One clinical trial, in adults in India, most of whom had been hospitalised with COVID-19, randomly assigned participants to either colchicine or matched placebo. The primary outcome measure was a 6-min-walk test. No effect of colchicine on cardiorespiratory function was found in either the primary or secondary outcomes. One other small trial evaluated the efficacy of famotidine against matched placebo on cognitive function in adults previously hospitalised with COVID-19, finding a marginal, significant effect on cognition in participants allocated to famotidine. The third trial evaluated the efficacy of apixaban prophylaxis in adults post-discharge from hospital following admission for COVID-19, finding that 14-day treatment with apixaban did not reduce re-admission or post-hospital mortality. We found no trials to date focusing on individuals not previously hospitalised with COVID-19, in whom the majority of the long COVID burden exists, or on fatigue, the most commonly reported symptom of long COVID.

Added value of this study

To our knowledge, this is the first and largest trial of rivaroxaban, colchicine, and antihistamines (famotidine–loratadine) in the management of fatigue in non-hospitalised adults with long COVID in the routine care context. In 778 adults, the primary outcome of self-reported fatigue, as measured with the Fatigue Assessment Scale, decreased across all participants in the first 3 months, including those assigned no drug who received usual care only. Marginal, additional decreases in fatigue were reported in recipients of colchicine and famotidine–loratadine, but not rivaroxaban, compared with no drug in adjusted analyses. No substantial differences in fatigue scores between groups were found at 24 weeks, 12 weeks after drug cessation.

Implications of all the available evidence

Considerable uncertainty exists on the use of repurposed drugs to treat long COVID. Treatment with either colchicine or famotidine–loratadine could offer marginal additional improvement of fatigue but these gains revert on drug cessation. Long-term symptom benefit in long COVID is unlikely with these drugs alone. Placebo-controlled trials with agreed consensus primary outcome measures in certain subgroups of individuals with long COVID could help targeting of repurposed drugs. Trials could also assess other repurposed drugs, combination therapies, and how care is delivered.

Introduction

Persistent symptoms following acute SARS-CoV-2 infection (post-acute sequelae of COVID-19 or post-COVID-19 condition [also known as long COVID]) affect 1–5% of working-age adults globally, with costs to health care, individuals, and economies.[1] In this heterogeneous disease, symptoms frequently include fatigue (often with post-exertional malaise), breathlessness, myalgia, and cognitive dysfunction (so-called brain fog),[2] with greater symptom burden and functional impairment in individuals with long COVID accessing specialist care who were not hospitalised for their original infection than in individuals without COVID-19[3] and individuals post-hospitalisation for COVID-19.[2] Fatigue most strongly predicted non-recovery in a previous study: less than 15% of people with long COVID and severe fatigue recovered over 2 years.[4] However, long COVID lacks precise clinical definitions, diagnostic tests, high-quality clinical trials, and approved treatments.[5] In 2020–21, the UK National Health Service (NHS) formed commissioning guidance and an integrated long COVID clinic network, providing specialist and community support.[6]

To our knowledge, few clinical trials to date have investigated individuals with long COVID who were not hospitalised for their original infection. Phase 2 studies have reported no efficacy of antivirals and experimental compounds for fatigue.[7–9] Uncontrolled case series and small trials have reported improved fatigue and cognitive function with H_1 and/or H_2 histamine receptor blockade (famotidine or fexofenadine).[10,11] In an open-label, randomised controlled trial in individuals after hospitalisation for COVID-19, a preprint reported no effect of apixaban on mortality or hospitalisation, but without fatigue or other outcome data.[12] A preprint, open-label case series of 91 individuals with long COVID reported improvement in fatigue with the triple therapy of aspirin, clopidogrel, and apixaban.[13] One trial reported no effect of colchicine against matched placebo on exercise tolerance (by 6-min-walk test [6MWT]) in predominantly adults hospitalised with COVID-19 with persistent symptoms and elevated C-reactive protein (CRP)[14] The efficacy of repurposed drugs for long COVID, particularly fatigue symptoms, in individuals who were not hospitalised with COVID-19 remains uncertain.

Acute, severe COVID-19 is characterised by dysregulated, multisystem inflammation that is improved by dexamethasone and baricitinib treatment.[15,16] Chronic immunopathology, including exercise-induced inflammatory myopathy,[17] is implicated in long COVID. Individuals with long COVID who were not hospitalised with COVID-19 have been shown to have reduced

exercise intolerance and endothelial dysfunction with increased thrombogenicity,[18,19] providing potential targets for colchicine and rivaroxaban. Even after mild initial illness, these processes can persist, possibly responding to repurposed drugs acting on the endothelium.

In this open-label, adaptive platform, phase 3, randomised controlled trial, nested within a pragmatic, multicentre, cluster-randomised trial of an integrated care pathway (ICP) for long COVID, we compared the efficacy and safety of three repurposed drugs in three drug classes (anti-inflammatory, antihistaminergic, and anticoagulant) with no drug for fatigue in adults with long COVID who had not previously been hospitalised with COVID-19.

Methods

Study design

The STIMULATE-ICP multisite, open-label, cluster-randomised controlled trial aimed to study the efficacy of two community-based components added to NHS specialist-led long COVID care in the UK compared with NHS specialist-led long COVID care alone (hereafter, usual care).[20] These additional components were: (1) multiorgan MRI (Coverscan [Perspectum, Oxford, UK]) and clinical decision support preceding usual care; and (2) community-based, digitally enabled, rehabilitation through an app (Living with COVID Recovery [Living With, Brighton, UK]). Usual care included clinical assessment and investigations, self-management, multidisciplinary rehabilitation for support with symptoms and pacing, and ongoing community support. Participants were randomly assigned in blocks at the cluster level, defined by strata based on population size and deprivation of their participating primary care network, to receive usual care plus multiorgan MRI with or without app-based rehabilitation, usual care plus app-based rehabilitation, or usual care only (figure 1). Participants were invited into an additional nested, adaptive platform, drug trial at first long COVID clinic review (figure 2; appendix pp 63–87).

Drug trial eligibility was initially restricted to first referral to one of six NHS long COVID clinics also participating in the cluster-randomised controlled trial.[20] There were five amendments to the original protocol for the cluster randomised controlled trial (RCT; appendix pp 28–32); the first (issued Jan 4, 2022) incorporated famotidine–loratadine combination in response to a combined review from the Medicines and Healthcare products Regulatory Agency (MHRA) and the Health Research Authority (HRA). The second (issued March 7, 2022) was for inclusion of colchicine and rivaroxaban and associated changes in analyses. The third (issued Dec 12, 2022) uncoupled the ICP trial from the drug trial by adding six drug arm-only sites that provided usual care but were unable to access Coverscan or the Living with COVID Recovery app, and was made due to challenges in drug trial recruitment. The fourth (issued June 9, 2023) covered inclusion of individuals with ongoing long COVID symptoms who had previously received long COVID care at any participating site before the drug trial, and an update for an urgent safety measure for famotidine (appendix p 280). The fifth amendment (issued Dec 19, 2024) changed the outcome of characterisation of pathophysiology, trajectory, health-care utilisation, and outcomes of long COVID from a secondary to an exploratory objective. In this Article, we report drug trial results (both ICP and drug-only sites). The cluster-randomised, ICP trial is reported separately.[21]

The cluster RCT and the drug trial were approved by the NHS HRA (IRAS 1004698), Research and Ethics Committee Wales (21/SC/0416), and the MHRA (CTA20363/0439/001-0002). Independent oversight was provided by both Trial Steering and Data Monitoring Committees. The trial was registered on May 30, 2022, with the International Standard Randomised Controlled Trial Number registry (ISRCTN10665760). Written informed consent was obtained from all participants. A patient and public involvement and engagement (PPIE) panel consisting of 11 volunteers with long COVID lived experience reviewed and contributed to all aspects of study design, attending regular study update meetings from design through to dissemination of results. The study is reported in line with CONSORT 2025 guidelines (appendix pp 272–78).

For the **STIMULATE-ICP trial registration** see https://www.isrctn.com/ISRCTN10665760

Participants

We included adults aged 18 years and older with long COVID, defined as persistent, post-COVID-19 symptoms for at least 4 weeks without alternative explanation, as established by a specialist clinician.[20] Exclusion criteria were previous COVID-19 hospitalisation; pregnancy, planning pregnancy, or breastfeeding; hypersensitivity to any study drugs; use of drugs contraindicated with study drug co-administration; severe renal failure or insufficiency (estimated glomerular filtration rate <10 mL/min) or severe liver dysfunction; and inability to give consent (appendix pp 77–80). Sex and ethnicity were self-reported by participants via the case report form, and participants provided written informed consent.

Randomisation and masking

By central, computer-generated block randomisation (with varying block sizes), participants were randomly assigned 1:1:1:1 to receive oral colchicine 500 µg twice daily, famotidine 40 mg once daily with loratadine 10 mg once daily, rivaroxaban 10 mg once daily, or no drug for 12 weeks. Randomisation was stratified by site, birth sex, ICP trial group allocation, and being a new or previous patient of a drug-only site. All participants received usual care. Like other large, pragmatic, COVID-19-era trials, including RECOVERY,[15] in which substantial service pressure necessitated rapid research delivery, we used an open-label, multi-arm design, evaluating multiple agents

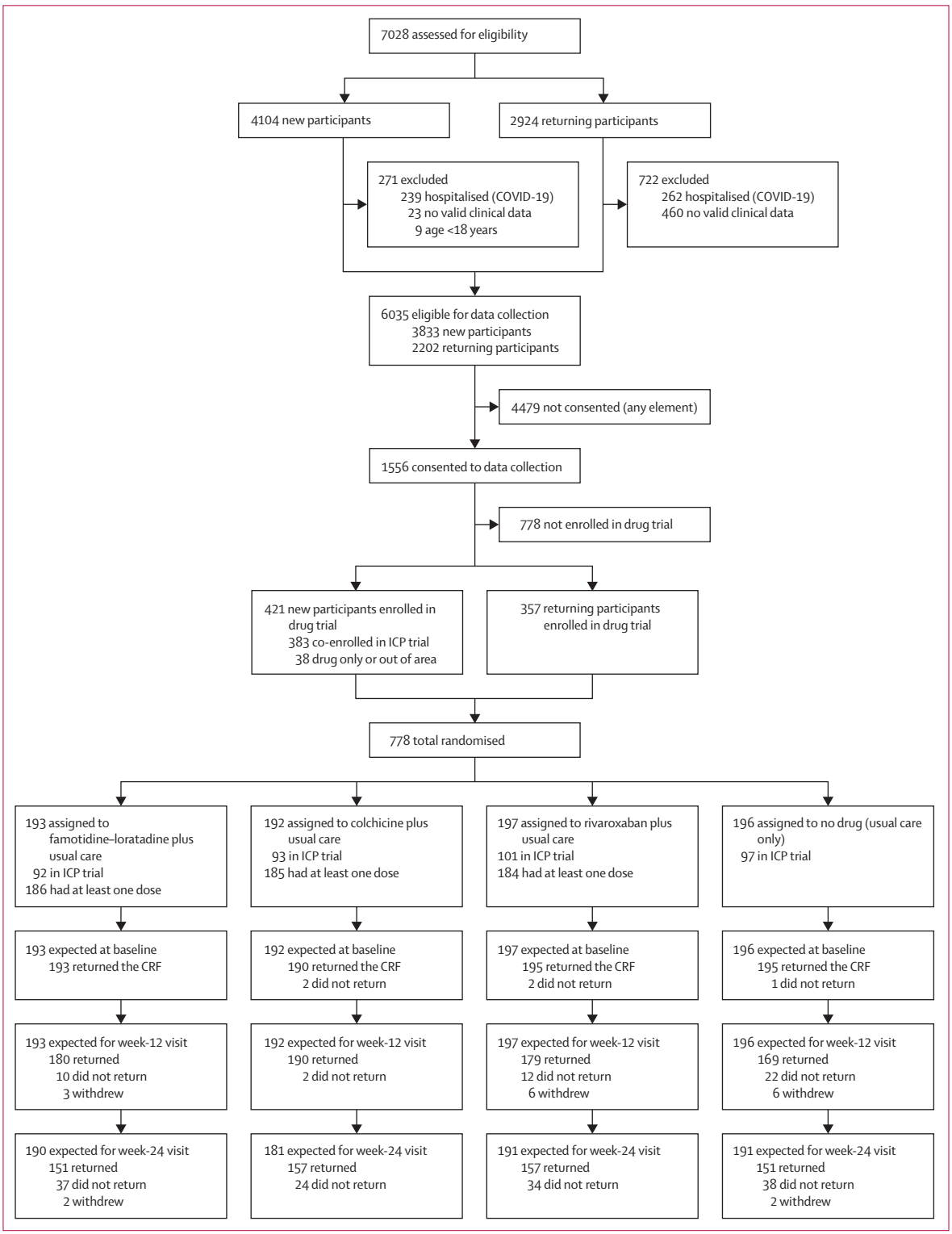

Figure 1: **Trial profile**

Completed case record forms were available and FAS scores analysed for >99% of participants at baseline (773 and 750 participants, respectively). 174 (93%) of 187 participants in the famotidine–loratadine group, 160 (86%) of 186 in the colchicine group, 171 (91%) of 188 in the rivaroxaban group, and 163 (86%) of 189 in the no drug (usual care only) group had calculable scores at baseline and 12 weeks and were included in the available case population for the primary endpoint. Completed case report forms were available and FAS scores were calculable at baseline and 24 weeks for 148 (79%) of 187 participants in the famotidine–loratadine group, 153 (82%) of 186 in the colchicine group, 152 (82%) of 188 in the rivaroxaban group, and 147 (79%) of 189 in the no drug (usual care only) group. CRF=case report form. FAS=Fatigue Assessment Scale. ICP=integrated care pathway.

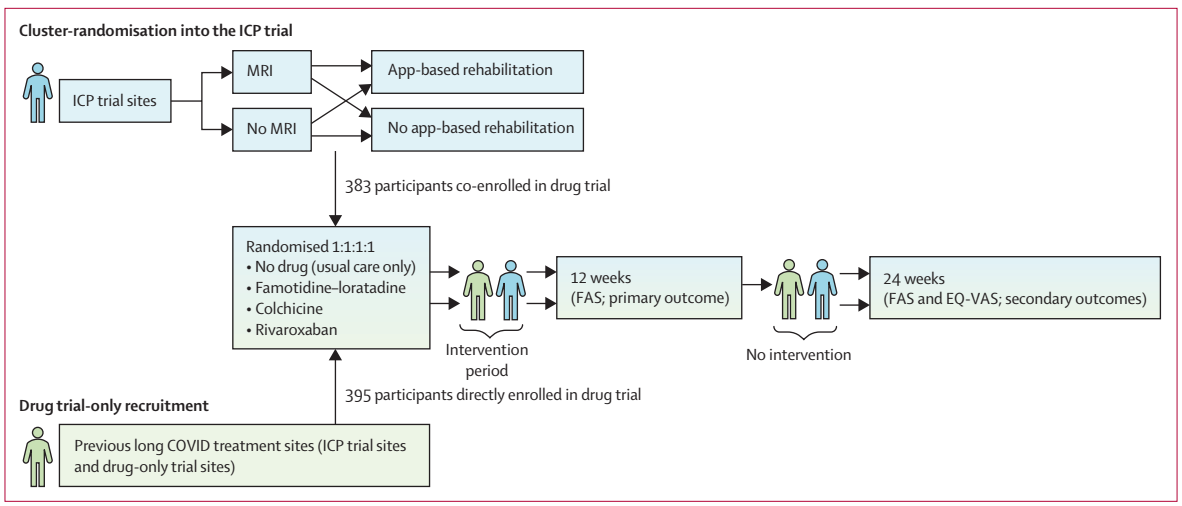

Figure 2: **Study schematic**
The trial design allowed recruitment of both new and returning participants. New participants were individuals who were new to long COVID clinic care before the trial. Returning participants were individuals who had already received long COVID clinic care before the trial. Data were analysed from a total of 778 participants, of whom 421 were recruited to sites hosting the ICP intervention study (of whom 383 were co-enrolled in the ICP intervention study and 38 were enrolled as a drug-only or out-of-area participants (ie, an individual who was recruited to a particular site in the ICP trial but was not from the catchment area of that clinic), and 357 participants were recruited to sites hosting drug-only trial participation. All participants received usual care, which was long COVID care led by a UK National Health Service specialist, and were seen at baseline, 12, and 24 weeks. EQ-VAS=EQ-5D-5L visual analogue scale. FAS=Fatigue Assessment Scale. ICP=integrated care pathway.

simultaneously. Our PPIE panel supported this trial design to meet patient needs and build participant trust, in the context of barriers to clinical care (eg, stigma) that risked poor trial engagement and under-recruitment.[22] Our design minimised the considerable complexity and lengthy, costly delays implicit in over-encapsulation of four different drugs and matched placebo. Analysts were masked to outcomes and allocations until data lock. Participants were unblinded to allocation throughout the trial, as were investigators after data lock.

Procedures

Participants were screened for eligibility and given trial information. After giving informed consent and undergoing random treatment allocation, participants completed standard case report forms, which were to be returned to trial practitioners within 7 days (appendix pp 146–88). Sex, gender, and ethnicity data were collected in the case report form along with baseline medications (including supplements and over-the-counter drugs). No restrictions were imposed on use of any drugs, except those with recognised interactions with an allocated drug, in which case a 7-day washout period was advised. If a participant was already taking one of the trial drugs, the same 7-day washout period was advised.

Trial researchers conducted visits (in person or via telephone) at weeks 12 and 24. Self-reported early cessation, adherence, and reasons for discontinuation were recorded at 12 weeks. Treatment could be discontinued for serious adverse events (SAEs) or drug intolerance. SAEs and adverse events were defined and assessed systematically (appendix pp 100–10), with clinician-adjudicated relatedness to study drugs.

The Fatigue Assessment Scale (FAS), a 10-point questionnaire for physical and cognitive fatigue with scores ranging from 10 (no fatigue) to 50 (debilitating fatigue) and defined improvement criteria,[23] was completed at baseline and weeks 12 and 24, as was the EQ-5D-5L visual analogue scale (EQ-VAS). EQ-VAS is a 100-point scale used to visually assess current health and wellbeing as a percentage of self-defined best health, where 0 is worst imaginable health and 100 is best health, which over 85% of patients can satisfactorily complete.[24] FAS and EQ-VAS were part of the case report form at baseline and then administered at 12 weeks by investigators over the phone or in person, or by postal and electronic link options, and at 24 weeks with the same options with the exception of in person.

Outcomes

Validated, objective metrics of recovery or patient-reported outcomes (PROM) for use in clinical trials, and validated classification tools for capturing clinical heterogeneity, are lacking for long COVID.[20,25] When the trial was designed in 2021, most people with long COVID reported severe, debilitating fatigue, associated with slower recovery and reduced quality of life.[2] Early reports of small changes in fatigue over the first 8 months after COVID-19 infection suggested that fatigue would be the most clinically meaningful primary outcome measure.[3,20,26] For consistency and bias reduction, we assessed fatigue using FAS, a PROM extensively used and validated in other fatigue-dominant, multisystem diseases (appendix pp 51–52, 61, and 178), as the 12-week primary outcome measure.[23] The minimally clinically important difference (MCID) in FAS scores is a change of more than 10%,[23] considered clinically

significant and beyond that expected by placebo effects or expectation bias alone. In a previous study in adults with long COVID,[4] the median FAS score at baseline was 33, such that a 3-point FAS score decrease would be approximately equivalent to a 10% change in the usual care group.

Secondary outcomes reported in this Article include the 24-week FAS score (12 weeks after drug cessation) and 12-week and 24-week EQ-VAS scores.[2] Other secondary outcomes (appendix pp 62, 178–87, and 217–19) will be analysed and reported after trial completion.

Statistical analysis

Full statistics details are in the statistical analysis plan (appendix pp 189–272); the software used was STATA SE version 18.5. To enable a coupled analysis of both drug and ICP elements of a 2×2 factorial trial, in 2021 we used clinic data and published reports of long COVID fatigue in 2020[2,26] to originally plan a sample size of up to 4520 participants, based on up to four (drug and usual care) parallel arms of up to 1130 evaluable participants each, to detect an interaction effect of 3 points on FAS with 90% power. Under-recruitment necessitated a partial decoupling of the cluster trial and drug trial, meaning that enrolment of 200 participants per active arm, with corresponding concurrent controls, would provide 85% power to detect a Cohen's *d* of 0·3 on FAS (difference between means in two treatment arms divided by the SD of the difference) at the 0·05 alpha level for each intervention arm, compared with usual long COVID care (appendix pp 214–15). No formal sample size inflation was made for loss to follow-up.

Analysis populations for efficacy and safety included all participants randomly assigned into the drug trial. To control for potential confounding from either ICP trial group allocation, site, previous management of long COVID, or time since symptom onset, participants randomly allocated to each drug arm were compared with those randomly allocated concurrently to no drug across all three populations to ensure contemporaneous usual long COVID care controls for each comparison. As each drug has a different mechanism of action, we used a non-familywise error-controlled design, or per-comparison error rate control. Therefore, we did not apply multiple-testing correction to results. A linear mixed-effects model for 12-week FAS score was applied, adjusting for baseline FAS score, with sex and treatment pathway as fixed effects and site as a random effect to control for ICP interventions and site variations in usual long COVID care. If there was poor convergence, site was instead fitted as fixed. Regression assumptions of normality, linearity, and homogeneity of variance were assessed through plots. We estimated treatment effect on 12-week FAS score for each drug compared with usual long COVID care, using the model coefficient, by available case analysis (ie, in participants with calculable FAS scores at baseline and 12 weeks). All reported p values are two sided and derived from the *t*-statistics for the model coefficients relative to zero. We applied the same model to all secondary outcome analyses.

We planned subgroup analyses for cardiorespiratory, neuropsychiatric, and mast-cell symptom subgroups and in individuals enrolled in both the drug trial and ICP trial. Post hoc, we hypothesised that trial drugs might have less effect in people with longer pretreatment symptom duration. We tested for an association between symptom duration and baseline FAS scores, finding only very small positive correlations ($R<0·15$) at baseline, 12 weeks, and 24 weeks. Even so, we adjusted the FAS outcome model to include symptom duration. Two prespecified sensitivity analyses were performed for the primary outcome: multiple imputation for the primary outcome; and an analysis population restricted to participants who completed the full 84 days allocation of medication versus control group participants who completed at least 84 days of follow-up.

Role of the funding source

The funder of the study had no role in study design, data collection, analysis, and interpretation, writing of the report, or the decision to submit for publication.

Results

Of 7028 potential participants screened, 6035 met inclusion criteria, and 1556 gave consent for data collection (figure 1). Of these, 778 declined to enrol in the drug trial. Reasons for non-consent and non-randomisation to the drug trial are detailed in the appendix (p 66). Between Aug 22, 2022, and Aug 7, 2024, 778 participants, 383 of whom were co-enrolled in the ICP trial and 395 (357 returning and 38 new) who were directly enrolled in the drug trial, were randomly assigned to the colchicine (n=192), famotidine–loratadine (n=193), rivaroxaban (n=197), or no drug (usual care only; n=196) groups (figure 1; appendix p 11). 185 (96%) of 192 participants in the colchicine group, 186 (96%) of 193 in the famotidine–loratadine group, and 184 (93%) of 197 in the rivaroxaban group took at least one allocated drug dose (figure 1). In the no drug group, 14 participants received a dose of off-label trial drug (six [3%] had famotidine, six [3%] had loratadine, and two [1%] had colchicine) during the trial (appendix p 12).

The mean age of participants was 46 years (SD 12·4). 495 (64%) of 778 participants were female and 283 (36%) were male, and 91 (12%) were from an ethnic group other than White (table 1). At baseline, asthma (17%), allergy (17%), and mental health conditions (31%) were common. Overall, 736 participants (97%) had received at least one COVID-19 vaccine dose at baseline. The median number of long COVID symptoms was nine (IQR 8–9), the mean baseline FAS score was 36·8 (SD 7·49), and the median symptom duration was 775 days (IQR 381–1163). Concurrent medications at recruitment were common,

particularly for depression (116 participants [15%]), asthma (108 [14%]), acid reflux (87 [11%]), pain (134 [17%]), supplements (230 [30%]), and long COVID symptom management (79 [10%]), but no trial drugs were routinely prescribed (table 1). The most commonly reported medications for long COVID symptom management were salbutamol, fostair, magnesium, famotidine, ibuprofen, fexofenadine, amitriptyline, cetirizine, N-acetylcysteine, nattokinase, and naltrexone.

Baseline demographics were similar across ICP and drug-only sites (appendix pp 13–14), including mean baseline FAS scores (36·4 [SD 7·6], 37·8 [8·2], and 37·0 [7·3] in ICP, new, and re-treated participants, respectively). Median duration of long COVID symptoms was longer in re-treated, drug-only participants (992 days, IQR 768–1355) and new drug-only or out of area participants (888 days, 745–1494) compared with ICP participants (408 days, 256–777).

750 participants completed the FAS at baseline (187 participants in the famotidine–loratadine group, 186 in the colchicine group, 188 in the rivaroxaban group, and 189 in the no drug group; table 2). 668 (86%) of those

	Colchicine (n=192)	Famotidine–loratadine (n=193)	Rivaroxaban (n=197)	No drug (usual care only; n=196)
Age, years	45·2 (13); n=192	46·1 (12); n=193	44·4 (12); n=197	47 (13); n=197
Sex at birth				
Female	121 (63%)	123 (64%)	127 (65%)	124 (63%)
Male	71 (37%)	70 (36%)	70 (36%)	72 (37%)
General practice Index of Multiple Deprivation quintile				
1 (most deprived)	40/184 (22%)	27/188 (14%)	36/191 (19%)	33/192 (17%)
2	47/184 (26%)	55/188 (29%)	53/191 (28%)	39/192 (20%)
3	35/184 (19%)	37/188 (20%)	37/191 (19%)	47/192 (25%)
4	33/184 (18%)	35/188 (19%)	35/191 (18%)	39/192 (20%)
5 (least deprived)	29/184 (16%)	34/188 (18%)	30/191 (16%)	34/192 (18%)
Ethnicity				
White	166/188 (88%)	166/192 (86%)	173/193 (90%)	169/192 (88%)
Mixed	11/188 (6%)	11/192 (6%)	6/193 (3%)	11/192 (6%)
Asian	5/188 (3%)	10/192 (5%)	11/193 (6%)	7/192 (4%)
Black	1/188 (<1%)	0	2/193 (1%)	1/192 (<1%)
Other	5/188 (3%)	5/192 (3%)	1/193 (<1%)	4/192 (2%)
BMI, kg/m²	25·9 (23·1–29·7); n=148	27·7 (24·8–33·0); n=139	27·4 (24·0–31·5); n=153	25·8 (23·3–30·1); n=139
Long COVID symptom duration, days	823 (408–1166); n=184	766 (399–1142); n=189	737 (372–1165); n=189	795 (37–1149); n=189
Number of long COVID symptoms	9·0 (7·0–9·0); n=186	9·0 (8·0–10·0); n=187	9·0 (8·0–9·0); n=190	9·0 (8·0–9·0); n=187
Breathlessness	158/181 (87%)	166/187 (89%)	162/190 (85%)	152/181 (84%)
Cough or throat symptoms	111/181 (61%)	117/185 (63%)	126/189 (67%)	120/183 (66%)
Fatigue	179/183 (98%)	180/182 (99%)	188/189 (>99%)	181/184 (98%)
Altered smell or taste	61/183 (33%)	69/186 (37%)	63/189 (33%)	70/185 (38%)
Pain or discomfort	174/184 (95%)	171/186 (92%)	181/189 (95%)	178/184 (97%)
Cognitive problems	176/185 (95%)	178/186 (96%)	184/190 (97%)	180/187 (96%)
Palpitations or dizziness	159/186 (86%)	152/186 (82%)	166/190 (87%)	165/187 (88%)
Crashing or relapse	173/186 (93%)	176/185 (95%)	180/189 (95%)	176/184 (96%)
Anxiety or mood problems	169/184 (92%)	175/185 (95%)	176/190 (93%)	175/187 (94%)
Poor sleep	158/187 (86%)	165/185 (89%)	170/189 (90%)	169/185 (91%)
Vaccinated against COVID-19	179/187 (96%)	184/192 (96%)	187/192 (97%)	189/192 (98%)
Medical history				
Depression	38/192 (20%)	45/193 (23%)	51/197 (26%)	40/195 (21%)
Anxiety	28/192 (15%)	33/193 (17%)	36/197 (18%)	33/195 (17%)
Both anxiety and depression	15/192 (8%)	20/193 (10%)	17/197 (9%)	15/195 (8%)
Hypertension	2/192 (1%)	9/193 (5%)	6/197 (3%)	5/195 (3%)
Allergies	28/192 (15%)	50/193 (26%)	39/197 (20%)	17/195 (9%)
Migraine	12/192 (6%)	17/193 (9%)	16/197 (8%)	20/195 (10%)
Asthma	24/192 (13%)	32/193 (17%)	41/197 (21%)	35/195 (18%)
Diabetes	3/192 (2%)	7/193 (4%)	8/197 (4%)	4/195 (2%)
Thyroid disorder	8/192 (4%)	14//193 (7%)	11/197 (6%)	12/195 (6%)

(Table 1 continues on next page)

	Colchicine (n=192)	Famotidine–loratadine (n=193)	Rivaroxaban (n=197)	No drug (usual care only; n=196)
(Continued from previous page)				
Indication for pre-existing drug treatment at enrolment				
Depression	20/192 (10%)	22/193 (11%)	38/197 (19%)	36/195 (19%)
Anxiety	9/192 (5%)	15/193 (8%)	13/197 (7%)	13/195 (7%)
Both anxiety and depression	11/192 (6%)	8/193 (4%)	9/197 (5%)	4/195 (2%)
Thyroid	9/192 (5%)	13/193 (7%)	13/197 (7%)	12/195 (6%)
Allergies	3/192 (2%)	4/193 (2%)	6/197 (3%)	2/195 (1%)
Asthma	19 /192 (10%)	24/193 (12%)	34/197 (17%)	31/195 (16%)
Cholesterol	2/192 (1%)	1/193 (1%)	5/197 (3%)	5/195 (3%)
Hypertension	9/192 (5%)	13/193 (7%)	12/197 (6%)	10/195 (5%)
Menopause or perimenopause	12/192 (6%)	20/193 (10%)	14/197 (7%)	17/195 (9%)
Post-COVID condition	23/192 (12%)	12/193 (6%)	18/197 (9%)	26/195 (13%)
Reflux	23/192 (12%)	15/193 (8%)	24/197 (12%)	25/195 (13%)
Pain	35/192 (18%)	27/193 (14%)	36/197 (18%)	36/195 (19%)
Supplement	58/192 (30%)	62/193 (32%)	53/197 (27%)	57/195 (29%)
Baseline laboratory results				
Haemoglobin, g/dL	141 (132–150); n=190	142 (133–150); n=192	140 (133–147); n=197	141 (132–148); n=194
White blood cell count, cells/mm^3	6·6 (5·5–7·7); n=190	6·5 (5·4–7·6); n=192	6·7 (5·4–8·0); n=197	6·4 (5·6–7·4); n=194
Platelet count, 10^9/L	268 (227–309); n=190	265 (231–306); n=193	268 (230–330); n=197	263 (226–298); n=194
ESR, mm/h	5 (2–9); n=36	5 (2–9); n=37	5 (2–9); n=31	5 (2–9); n=38
Creatinine, µmol/L	70 (63–80); n=188	71 (62–81); n=190	70 (63–81); n=192	72 (65–81); n=191
Alanine aminotransferase, IU/L	23 (16–32); n=188	21 (17–32); n=191	22 (16–33); n=192	22 (16–31); n=191
Total cholesterol, mmol/L	5·4 (4·4–6·0); n=86	5·0 (4·6–5·8); n=104	5·2 (4·4–5·8); n=109	5·0 (4·5–5·7); n=96
C-reactive protein, mg/L	1·8 (0·7–4·3); n=134	1·3 (0·8–5·0); n=131	1·6 (0·6–5·0); n=144	1·9 (0·8–5·0); n=137
Thyroid stimulating hormone, IU/L	1·7 (1·3–2·1); n=122	1·7 (1·3–2·2); n=125	1·5 (1·1–2·2); n=134	1·7 (1·1–2·3); n=130

Data are mean (SD); number of participants, n/N (%), or median (IQR); number of participants. ESR=erythrocyte sedimentation rate.

Table 1: **Baseline characteristics of all randomly assigned participants**

participants (174 in the famotidine–loratadine group, 160 in the colchicine group, 171 in the rivaroxaban group, and 163 in the no drug group) had a calculable FAS score at 12 weeks, of whom 652 (156 in the colchicine group, 171 in the famotidine–loratadine group, 165 in the rivaroxaban group, and 160 in the no drug group) also had a calculable FAS score at baseline. We observed a clinically relevant reduction in mean FAS scores at 12 weeks of 4·3 points (from 36·8 [SD 7·49] to 32·5 [9·13]) across all trial arms, with heterogeneity in response, but with most participants having a substantial reduction (appendix p 23). Within arms, mean FAS score reductions from baseline to 12 weeks were 4·4 points (36·2 [SD 7·71] to 31·8 [9·83]) for colchicine, 4·8 points (36·5 [8·21] to 31·7 [9·19]) for famotidine–loratadine, 4·4 points (36·9 [6·81] to 32·5 [8·90]) for rivaroxaban, and 3·3 points (37·5 [7·17] to 34·2 [8·41]) for the no drug group, all meeting the MCID definition. After adjusting for baseline FAS score, sex, ICP allocation, and trial site across arms, receiving either colchicine (–1·49 points [95% CI –2·92 to –0·06]; p=0·041) or famotidine–loratadine (–1·48 [–2·88 to –0·08]; p=0·038), but not rivaroxaban (–1·06 [–2·47 to 0·35]; p=0·139), was associated with small, additional 12-week FAS score reductions relative to the no drug group (table 3, figure 3). Due to poor convergence, site was fitted as fixed in linear regression models. After adjusting for baseline FAS score and other covariates, only two sites (6 and 8) had significantly different 12-week FAS scores compared with the reference site (site 5, as the largest site, which recruited over 50% of the entire trial population; table 3).

Compared with the no drug (usual care only) group, FAS scores at 24 weeks (12 weeks after drug cessation) were –0·043 points (95% CI –1·53 to 1·44; p=0·96) in the colchicine group, 0·34 (–1·16 to 1·83; p=0·66) for famotidine–loratadine, and 0·04 (–1·45 to 1·53; p=0·96) in the rivaroxaban group (figure 3; appendix p 18).

Within arms, mean FAS score reductions from baseline to 24 weeks were 3·5 points (36·2 [SD 7·71] to 32·7 [9·74]) for colchicine, 3·1 points (36·5 [8·21] to 33·4 [8·92]) for famotidine–loratadine, 3·5 points (36·9 [6·81] to 33·4 [8·92]) for rivaroxaban, and 3·4 points (37·5 [7·17] to 34·1 [8·51]) for the no drug group, all meeting the MCID definition.

Mean EQ-VAS scores at baseline were 54·4 (SD 22·2), 55·0 (20·5), 52·6 (21·9), and 47·7 (20·9) in the colchicine, famotidine–loratadine, rivaroxaban, and no drug groups, respectively. At 12 weeks, EQ-VAS scores were 4·13 points

	Colchicine (n=192)	Famotidine–loratadine (n=193)	Rivaroxaban (n=197)	No drug (usual care only; n=196)
FAS score before long COVID	15·8 (5·32); n=187	15·6 (5·09); n=188	16·5 (5·41); n=187	16·2 (5·26); n=190
FAS score at baseline	36·2 (7·71); n=186	36·5 (8·21); n=187	36·9 (6·81); n=188	37·5 (7·17); n=189
Week 12 FAS score	31·8 (9·83); n=160	31·7 (9·19); n=174	32·5 (8·90); n=171	34·2 (8·41); n=163
Week 24 FAS score	32·7 (9·74); n=153	33·4 (8·92); n=148	33·4 (8·73); n=152	34·1 (8·51); n=147

Data are mean (SD); number of participants. Data for before the long COVID diagnosis were self-reported by participants. FAS=Fatigue Assessment Scale.

Table 2: **FAS scores across allocation groups from before long COVID diagnosis and at baseline, 12 weeks, and 24 weeks**

(95% CI 0·58–7·69; p=0·023), 4·84 points (1·36–8·32; p=0·006), and 3·5 points (0·034–7·01; p=0·048) higher in the colchicine, famotidine–loratadine, and rivaroxaban groups, respectively, compared with the no drug group (appendix pp 19 and 24). At 24 weeks, EQ-VAS scores in drug arms were not substantially changed from 12 weeks, but in the no drug group the EQ-VAS score had increased to be similar to the drug groups (appendix pp 20 and 24).

754 (97%) of 778 participants had symptom data available, of whom 750 (96%) were classified in all three symptom subgroups, one was classified in both cardiorespiratory and mast-cell activation subgroups but not in the neuropsychiatric symptoms subgroup, and only three had neither cardiorespiratory nor mast-cell activation symptoms. This almost complete overlap of symptom subgroups made the planned subgroup analysis futile. The other planned subgroup analysis of individuals in the drug trial versus those in the ICP trial was not done because our sample size was greatly underpowered for assessing drug trial versus cluster trial effects. In a post-hoc analysis, after adjustment of the FAS outcome model to include symptom duration, estimated changes in mean FAS scores in the drug groups compared with the no drug group at 12 weeks were –1·71 points (95% CI –3·15 to –0·27; p=0·020) for colchicine, –1·44 (–2·84 to –0·04; p=0·044) for famotidine–loratadine, and –1·02 (–2·44 to 0·40; p=0·158) for rivaroxaban (appendix p 21). The effect size estimated by the model coefficient for every additional year of long COVID was 0·46 (95% CI –0·05 to 0·98; p=0·078).

Results of the primary analysis and the multiple imputation sensitivity analysis were broadly similar, although there were no significant differences between the colchicine or famotidine–loratadine groups versus the no drug group in the sensitivity analysis (appendix p 22). In the sensitivity analysis restricted to individuals completing the full 84-day medication allocation, findings for 12-week FAS scores were consistent in size and direction as the primary analysis but no longer significant at the 5% level (colchicine –1·70 points [95% CI –3·51 to 0·11; p=0·066]; famotidine–loratadine –1·60 [–3·35 to 0·16; p=0·075]; and rivaroxaban –0·70 [–2·35 to 0·94; p=0·40]; appendix p 23).

199 (26%) of 778 participants reported an adverse event, including 57 (30%) of 192 participants in the colchicine group, 51 (26%) of 193 participants in the famotidine–loratadine group, 70 (36%) of 197 participants in the rivaroxaban group, and 21 (11%) of 196 participants in the no drug (usual care only) group (appendix p 12). For all participants, the median number of adverse events per participant was 0 (IQR 0–1). Most adverse events were mild or moderate in severity (appendix p 16). Gastrointestinal adverse events were reported in 27 (14%) participants in the colchicine group and minor bleeding or menorrhagia was reported in 26 (13%) participants in the rivaroxaban group (appendix pp 12 and 15–17). Ten SAEs were recorded in eight (1%) of 778 participants,

	Coefficient (95% CI)	p value
FAS at baseline	0·856 (0·787 to 0·925)	<0·001
Female sex at birth*	0·529 (0·521 to 1·579)	0·32
Disaggregated trial arms (fixed)†		
ICP study: multiorgan MRI plus digital rehabilitation arm	0·859 (–1·102 to 2·820)	0·39
ICP study: multiorgan MRI-only arm	1·002 (–1·100 to 3·104)	0·35
ICP study: digital rehabilitation-only arm	0·287 (–1·726 to 2·299)	0·78
Returning participant (any site)	1·290 (–0·440 to 3·021)	0·14
Drug only site: new participant or out of area	1·135 (–1·511 to 3·781)	0·40
Trial sites (site 5 used as reference)		
Site 1	0·741 (–2·009 to 3·491)	0·60
Site 2	0·380 (–2·329 to 3·088)	0·78
Site 3	0·543 (–0·927 to 2·013)	0·47
Site 4	–2·784 (–9·219 to 3·652)	0·40
Site 6	–2·544 (–4·599 to –0·489)	0·015
Site 7	0·196 (–3·729 to 4·121)	0·92
Site 8	2·655 (0·189 to 5·121)	0·035
Site 9	1·817 (–1·417 to 5·050)	0·27
Site 10	–0·053 (–2·782 to 2·676)	0·97
Site 11	–1·891 (–5·522 to 1·739)	0·31
Site 12	–0·730 (–3·604 to 2·145)	0·62
FAS in recipients of colchicine relative to no drug (usual care only)	–1·490 (–2·920 to –0·060)	0·041
FAS in recipients of famotidine–loratadine relative to no drug (usual care only)	–1·477 (–2·875 to –0·078)	0·038
FAS in recipients of rivaroxaban relative to no drug (usual care only)	–1·063 (–2·471 to 0·346)	0·14
Constant	0·788 (–2·418 to 3·993)	0·63

All p values are to two signficant figures, two sided, and derived from the *t*-statistics for the model coefficients which reflect the mean difference in FAS. FAS=Fatigue Assessment Scale. ICP=integrated care pathway. *Reference is male sex at birth. †Reference is the usual care only group.

Table 3: **Linear effects model showing effect size of trial drugs on FAS score at week 12 compared with usual care**

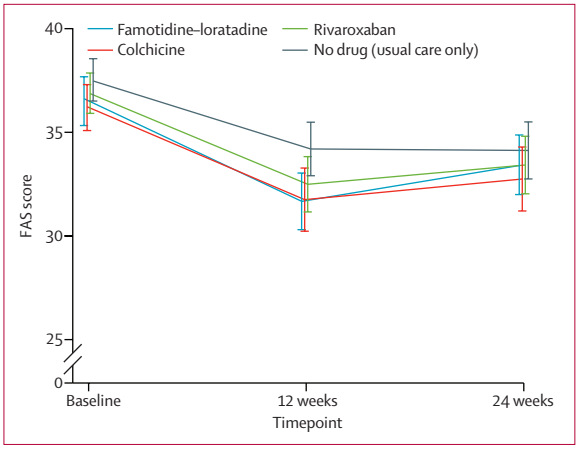

Figure 3: **Mean FAS scores and 95% CIs at baseline, 12 weeks, and 24 weeks, by allocation group**
FAS scores were collected at recruitment into drug trial arms, and at 12 weeks (approximately 3 months after starting treatment) and 24 weeks (approximately 6 months after recruitment, 3 months after treatment cessation). Not all participants contributed data at each timepoint. FAS ranges from 10–50; included scores are in the range of 20–50 points as scores <21 are considered normal (no fatigue) and so are not shown. Scores of 22–34 indicate the presence of fatigue; scores >34 indicate extreme fatigue. Points indicate mean FAS scores across participants by drug allocation; error bars indicate standard deviation. Lines connecting timepoints are shown to illustrate FAS trajectory. FAS=Fatigue Assessment Scale.

with five SAEs in three (2%) of 197 patients treated with rivaroxaban (appendix p 12). All SAEs required hospitalisation and were unrelated to trial drugs (appendix p 17).

Discussion

In this trial—to our knowledge, the largest, multicentre, long COVID clinical trial to date—we found that fatigue decreased and quality of life improved in all participants over 3 months, including those allocated to the no drug (usual care only) group. Additional, marginal fatigue reductions compared with the no drug group were reported by individuals receiving colchicine or famotidine–loratadine, but not rivaroxaban, at 12 weeks, reverting to equivalence with the no drug group at 24 weeks (12 weeks after drug cessation). Overall, our data do not support widespread clinical use of these drugs for fatigue reduction in long COVID, but our study does provide a framework to support second-generation, precision medicine, placebo-controlled trials of new and repurposed drugs and drug combinations for long COVID-associated fatigue.

All participants reported a change in FAS score at 12 weeks beyond the MCID, including those in the no drug group, potentially highlighting the importance of high-quality specialist care, including rehabilitation and pacing support, in obtaining meaningful clinical improvement. The similarity in reduction in FAS at 24 weeks (shown in the means or percentages) and MCID reduction explains why the differences between the drug groups and usual care group are no longer significant by 24 months. Our report of improvement in fatigue with usual long COVID care provided by specialist NHS clinics is in line with our previous observational evaluation of UK services,[4] and serves as an important addition to growing evidence supporting a multifaceted approach to long COVID rehabilitation. Our trial was done across 12 sites with broadly consistent care models, informed by NHS long COVID guidelines, in a broadly UK-representative population.[1] All sites were led by clinicians with long COVID expertise, and all provided rehabilitation advice and support in addition to the trial interventions. Beyond care components as outlined in NHS England commissioning guidance,[6] we cannot characterise which specific elements might have contributed most to observed changes in fatigue, nor the extent to which observed benefits might be attributable to being in a clinical trial. However, the long symptom duration and high baseline FAS scores in our participants argue against FAS score reduction being due to spontaneous recovery alone, as observed fatigue reductions were of greater magnitude than observed in contemporaneous longitudinal data from non-specialist centres.[26] People with long COVID frequently report several barriers, including stigma, to accessing appropriate care.[22] The consistent decrease in FAS scores beyond the MCID across all groups shows the importance of access to and evaluation of specialist care and support in long COVID management, as in other long-term conditions.[1,2,4]

In the few therapeutic long COVID trials to date, most have used self-reported overall health as a primary outcome measure, via different PROMS, since objective, validated clinical or laboratory biomarkers are lacking. These include studies of nirmeltrivir–ritonavir, which did not improve self-reported best health or fatigue,[7,27–29] and two placebo-controlled, phase 2 trials of investigational medical products SIM01 and AXA1125, in which participants reported modest but significant fatigue improvement.[8,9] Colchicine has well described, short-term anti-inflammasome activity, with effects on endothelial and myocardial inflammation, potentially relevant to long COVID. With more participants than these two phase 2 trials, one randomised controlled trial of colchicine versus matched placebo in mainly adults who had been hospitalised for their index SARS-CoV-2 infection, with biochemical evidence of inflammation (CRP >5·0 mg/dL) and prolonged symptoms, compared 6MWT results, testing whether treatment of systemic inflammation would translate to improved exercise tolerance.[14] No difference in 6MWT results was observed between groups throughout follow-up, nor were there any differences between allocation groups in the secondary outcome measurements at 12 and 52 weeks, which included a measure of fatigue, but these participants were not receiving specialist long COVID or rehabilitation support.[14] Although the 6MWT is a well validated measure of cardiovascular and respiratory

function, it should only be applied to people able to walk for 6 min; individuals with the most severe fatigue or fluctuating symptoms risk exacerbation of post-exertional malaise. Therefore, it is not recommended in routine clinical practice. The 6MWT does not have an established MCID in long COVID, further limiting interpretation of the observed mean difference of 5·6 m between allocation groups in the colchicine trial.[14] Finally, use of the Post COVID-19 Functional Status Scale as an inclusion criterion in that study might have increased the heterogeneity of trial participants, potentially limiting the observation of a treatment effect mediated by inflammatory reduction (as elevated CRP could have had other causes beyond long COVID) and a comparison with our trial. Overall, further data from placebo-controlled trials powered for patient-relevant endpoints are required to assess the clinical utility of colchicine in long COVID.

Self-reports of symptomatic efficacy from patients and a small uncontrolled observational study postulating benefit led us to include famotidine.[10] A subsequent small trial in a different patient population suggested that famotidine could improve cognitive function following acute severe COVID-19.[11] The antihistamine combination of famotidine–loratadine is unlikely to act by suppression of allergic symptoms: prevalence of self-reported allergic symptoms in this study was similar to national UK surveys,[30] and allergy is not a typical cause of fatigue. Modification of mast-cell mediated inflammation or vasodilation is a putative mechanism of action but, due to inadequate statistical power, we were unable to conduct planned symptom subtype analyses. Our findings support evaluation of famotidine or H_1 and H_2 antagonists in placebo-controlled trials.

Observational and experimental data supported evaluation of anticoagulants for long COVID treatment. Reported abnormalities in complement and platelet systems and blood detection of fibrinoid–amyloid complexes in people with long COVID have led to widespread off-label use of antiplatelet and direct-acting oral anticoagulants.[13] Amid concerns that anticoagulant-associated bleeding, particularly menstrual loss in women, could worsen fatigue, we evaluated low-dose rivaroxaban. Although we cannot exclude efficacy in certain individuals, our results do not support widespread prophylactic anticoagulation use in long COVID.

Long COVID is a clinically defined and highly heterogeneous disease. The observed small drug effect sizes in this all-comers trial could be confounded by placebo or expectation effects or mask smaller subgroups or endotypes that might or might not benefit from the interventions tested. We were unable to prestratify patients for randomisation to particular allocation groups due to a lack of validated tools to support this approach and the risk of introducing further bias in this open-label trial. Work planned a priori as one of the trial's secondary objectives—to characterise subgroups of responders and non-responders and describe phenotypical and/or biochemical characteristics—is ongoing (appendix pp 240–46).[20] We observed small FAS score reductions of similar magnitude overall across trial arms in a heterogeneous long COVID cohort, reverting to equivalence with the no drug control group at 24 weeks following treatment cessation, suggesting any potential effects (including placebo, trial, or non-specific effects) were transient and not disease-modifying. We cannot exclude that a subgroup could benefit from these drugs, but our results do not support their use in all individuals with long COVID.

The overall STIMULATE-ICP programme was designed to provide evidence for drugs and care pathways for long COVID in a pandemic setting. The challenges of undertaking a trial of this size and scope for a newly defined disease should not be underestimated. This Article is an important resource for future design of large-scale long COVID trials and other conditions characterised by debilitating fatigue, such as myalgic encephalomyelitis/chronic fatigue syndrome. A Delphi consensus, published 2 years after this trial was designed, proposed use of the Medical Research Council dyspnoea scale in long COVID, but no agreement was reached regarding outcome measures capturing any other major long COVID symptoms, including fatigue.[31] We chose not to include unvalidated and potentially biased assessments of activity, including wearable device data, as these have not been fully evaluated in clinical trials and risk confounding individual clinical advice, such as pacing, provided as part of usual long COVID care.

We chose an open-label design in this publicly funded trial, supported by the funder, our PPIE team, and ethical committee, with two aims: (1) to avoid estimated delays of 1 year and excessive costs (estimated £1 million) of developing placebo controls matched across all trial arms; and (2) to retain the trust of our patient population, many of whom experienced substantial stigma and barriers to care, reducing their trust in researchers and clinicians.[22] Our pragmatic protocol adjustments (appendix pp 28–32) allowed successful trial completion, despite a shifting clinical landscape during the pandemic that included COVID-19 vaccination introduction, falling hospitalisations, and new SARS-CoV-2 variants—all affecting long COVID clinical presentation and care. All participants had clinically validated long COVID diagnoses with substantial symptom duration and severe fatigue at recruitment, adding to generalisability and applicability of our findings.

However, our study has several limitations, reflecting both the changing nature of clinical services over the course of the trial and the needs of the patient population with whom the trial was co-designed. Although we controlled for cluster allocation in the analyses, including changes in usual long COVID care during the trial by stratification to participants contemporaneously randomly allocated to drug or usual long COVID care.

However, we cannot fully exclude additional confounding from ICP interventions in co-enrolled participants. FAS is a well validated PROM[32] in long COVID with a standardised scale but can be subject to day-to-day variation and potential bias. All our participants met the MCID for FAS at 12 weeks of 10%, including those in the no drug (usual care only) group, which was unexpected. Observed drug effects on FAS scores extended beyond the MCID when compared with usual care at 12 weeks, but these were of marginal clinical significance. We adjusted for baseline FAS scores in the primary outcome analysis and conducted sensitivity analyses to test for drug effects on FAS scores according to time since symptom onset to control as much as possible for heterogeneity in fatigue severity at baseline. Observational data suggest long COVID symptoms can worsen with repeated infections and improve after COVID-19 vaccination.[33] However, we were unable to retrospectively disaggregate effects of sequential SARS-CoV-2 exposures, repeated infection, or vaccination on FAS scores. Concealment was unfeasible for a trial of this size and complexity. Instead, we controlled for demographics, deprivation, site, and cluster allocation. We are unable to exclude placebo effects or expectation bias in our open-label trial, which substantially limits interpretation of results. In several, randomised, placebo-controlled long COVID clinical trials with short trial durations, preliminary results suggested symptom improvement across study arms, including placebo, which could account for our observed FAS score changes across all arms, rather than the effect of integrated long COVID care.[9,32] We anticipated a potential placebo effect, particularly with rivaroxaban, given widespread publicity regarding micro-embolic phenomena as a potential cause of long COVID.[13] Overall, our trial was designed to minimise systematic placebo effects or provider bias by randomising across 12 trial sites, but placebo-controlled trials are needed to further investigate our findings.

The STIMULATE-ICP trial shows that long-term symptom benefit in long COVID is unlikely with these drugs alone. We provide evidence in support of comprehensive clinical management pathways, including multifaceted rehabilitation, as the foundation of care for long COVID, and highlight some of the challenges of conducting trials in a rapidly shifting clinical landscape. Until pathophysiological mechanisms and precision medicine tools are better elucidated, future trials should evaluate synergy between individual care components for long COVID and pharmacological agents as the optimal management strategy. Our findings, including reversion of drug effect on cessation, justify investment in further platform studies of new and repurposed medicines as mechanistic understanding of long COVID evolves. It is also important to evaluate the contribution of how care is delivered using patient-led, clinically meaningful outcomes.

Contributors

ECW drafted the first manuscript draft, with editing and input from AB and MJH. GP, CB, and ST directly accessed and verified the data, and generated the data tables and figures from the trial database. Input was then sought from the wider writing committee; edits and changes were incorporated. ECW, MJH, and AB finalised the manuscript and prepared for publication. Writing group members had full access to all of the data in the study. All authors of the STIMULATE-ICP consortium reviewed and made comments on the manuscript and had final responsibility for the decision to submit for publication.

Declaration of interests

ECW participated in the Data Safety and Monitoring Board for the RECLAIM trial. RAE received payments from the UK Covid Inquiry and Scottish Covid Inquiry; a grant from Genentec/Roche; and speaker fees from BMJ Best Practice and Moderna; and was Chair of the European Respiratory Society Group 01.02 Pulmonary Rehabilitation and Chronic Care (2023–26), Chair of the American Thoracic Society Pulmonary Rehabilitation Assembly (2022–25), and a member of the ATS Pulmonary Rehabilitation Assembly Nominating Committee (2025–27). All other authors declare no competing interests.

Data sharing

Anonymised data (and supporting materials) are held at University College London (London, UK). Access will be available by application from late 2026 to the Chief Investigator (AB) by email or via the study website (https://www.stimulate-icp.org/) for observational research studies concerning long COVID with investigator support, and a data dictionary defining each field in the dataset will also be available on request. Applications will be considered and approved by the trial steering committee, and a signed data access agreement will be required to access the data at University College London. Data access will be for the full duration of any planned analyses from start to publication, as applicable.

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