Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial

RECOVERY Collaborative Group*

Summary

Background Many patients with COVID-19 have been treated with plasma containing anti-SARS-CoV-2 antibodies. We aimed to evaluate the safety and efficacy of convalescent plasma therapy in patients admitted to hospital with COVID-19.

Methods This randomised, controlled, open-label, platform trial (Randomised Evaluation of COVID-19 Therapy [RECOVERY]) is assessing several possible treatments in patients hospitalised with COVID-19 in the UK. The trial is underway at 177 NHS hospitals from across the UK. Eligible and consenting patients were randomly assigned (1:1) to receive either usual care alone (usual care group) or usual care plus high-titre convalescent plasma (convalescent plasma group). The primary outcome was 28-day mortality, analysed on an intention-to-treat basis. The trial is registered with ISRCTN, 50189673, and ClinicalTrials.gov, NCT04381936.

Findings Between May 28, 2020, and Jan 15, 2021, 11558 (71%) of 16287 patients enrolled in RECOVERY were eligible to receive convalescent plasma and were assigned to either the convalescent plasma group or the usual care group. There was no significant difference in 28-day mortality between the two groups: 1399 (24%) of 5795 patients in the convalescent plasma group and 1408 (24%) of 5763 patients in the usual care group died within 28 days (rate ratio 0·99, 95% CI 0·93–1·03; p=0·57). Among those not on invasive mechanical ventilation at randomisation, there was no significant difference in the proportion of patients meeting the composite endpoint of progression to invasive mechanical ventilation or death (1568 [29%] of 5493 patients in the convalescent plasma group vs 3822 [66%] patients in the usual care group; rate ratio 0·99, 95% CI 0·94–1·03; p=0·57). The 28-day mortality rate ratio was similar in all prespecified subgroups of patients, including in those patients without detectable SARS-CoV-2 antibodies at randomisation. Allocation to convalescent plasma had no significant effect on the proportion of patients discharged from hospital within 28 days (3832 [66%] patients in the convalescent plasma group vs 3822 [66%] patients in the usual care group; rate ratio 0·99, 95% CI 0·94–1·03; p=0·57). Among those not on invasive mechanical ventilation at randomisation, there was no significant difference in the proportion of patients meeting the composite endpoint of progression to invasive mechanical ventilation or death (1568 [29%] of 5493 patients in the convalescent plasma group vs 1568 [29%] of 5448 patients in the usual care group; rate ratio 0·99, 95% CI 0·93–1·05; p=0·79).

Interpretation In patients hospitalised with COVID-19, high-titre convalescent plasma did not improve survival or other prespecified clinical outcomes.

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plasma might reduce mortality in severe viral respiratory infections evidence from randomised trials remains scarce and inconclusive. Convalescent plasma has been used widely outside of clinical trials, including by more than 100,000 patients in the US Food and Drugs Administration (FDA) Expanded Access Program. An observational analysis of 3082 patients in this programme reported that in patients who had not received mechanical ventilation, 30-day mortality was lower in those transfused with higher-titre plasma (containing higher concentrations of anti-SARS-CoV-2 spike IgG) compared with those who received lower-titre plasma. A number of randomised trials of convalescent plasma in patients hospitalised with COVID-19 have been reported, but these trials have all been small and inconclusive. Moreover, patients who are hospitalised with COVID-19 are heterogeneous and any benefit of convalescent plasma could depend on the stage of disease, perhaps being restricted to those with milder disease early in the course of their illness or those who have not mounted an effective antibody response. Therefore, the efficacy of convalescent plasma as a treatment for patients hospitalised with COVID-19 is uncertain. We aimed to evaluate the efficacy and safety of convalescent plasma in patients hospitalised with COVID-19.

Methods
Study design and participants
The RECOVERY trial is an investigator-initiated, individually randomised, controlled, open-label, adaptive platform trial to evaluate the effects of potential treatments in patients hospitalised with COVID-19. Details of the trial design and results for other evaluated treatments (dexamethasone, hydroxychloroquine, lopinavir–ritonavir, azithromycin, and tocilizumab) have been published previously. The trial is underway at 177 NHS hospital organisations in the UK (appendix pp 5–28), supported by the National Institute for Health Research Clinical Research Network. The trial was coordinated by the trial sponsor, the Nuffield Department of Population Health, University of Oxford (Oxford, UK). The trial is being done in accordance with the principles of the International Conference on Harmonisation–Good Clinical Practice guidelines and approved by the UK Medicines and Healthcare products Regulatory Agency and the Cambridge East Research Ethics Committee (20/EE/0101). The protocol, statistical analysis plan, and additional information are available online and in the appendix (pp 66–151).

Hospitalised patients of any age were eligible for the trial if they had clinically suspected or laboratory-confirmed SARS-CoV-2 infection and no medical history that might, in the opinion of the attending clinician, put them at significant risk if they were to participate in the trial. Written informed consent was obtained from all patients or from their legal representative if they were too unwell or unable to provide consent.

Implications of all the available evidence
For patients admitted to hospital with COVID-19, convalescent plasma offers no material therapeutic benefits.
Until Sept 18, 2020, eligible and consenting patients were randomly assigned (1:1) to receive either usual care (usual care group) or usual care plus convalescent plasma (convalescent plasma group). From Sept 18, 2020, patients were randomly assigned (1:1:1) to the usual care group, convalescent plasma group, or to receive usual care plus REGN-COV2 (a combination of two monoclonal antibodies directed against SARS-CoV-2 spike protein; appendix pp 35–37). The REGN-COV2 evaluation is ongoing and not reported here. Random assignment was unstratified and done by local clinical or research staff using a web-based interface with allocation concealment (appendix pp 33–34). For some patients, convalescent plasma was either declined, unavailable at the trial site at the time of enrolment, or considered in the opinion of the attending doctor to be definitely contraindicated (eg, known moderate or severe allergy to blood components). These patients were not included in the comparison of convalescent plasma versus usual care.

In a factorial design, patients could be simultaneously randomly assigned to other treatment groups: (1) hydroxychloroquine or dexamethasone or azithromycin or lopinavir–ritonavir or colchicine versus usual care, and (2) aspirin versus usual care (appendix pp 33–34). The trial also allowed a subsequent randomisation for patients with progressive COVID-19 (evidence of hypoxia and a hyperinflammatory state) to tocilizumab versus usual care. Participants and local study staff were not masked to the allocated treatment. Several of these treatment groups were added to or removed from the protocol over the period that convalescent plasma was evaluated (appendix pp 29–34). The trial steering committee, investigators, and all other individuals involved in the trial were masked to outcome data during the trial.

**Procedures**
Convalescent plasma donors were recruited and screened by the four UK blood services: NHS Blood and Transplant, the Northern Ireland Blood Transfusion Service, the Scottish National Blood Transfusion Service, and the Welsh Blood Service (appendix pp 2–4, 29). Only plasma donations with a sample to cutoff ratio of 6·0 or more on the EUROIMMUN IgG enzyme-linked immunosorbent assay (ELISA) targeting the spike glycoprotein (PerkinElmer, London, UK) were supplied for the RECOVERY trial (appendix pp 29–34). The trial steering committee, investigators, and all other individuals involved in the trial were masked to outcome data during the trial.

**Outcomes**
Outcomes were assessed at 28 days after randomisation, with additional analyses specified at 6 months. The primary outcome was all-cause mortality. Secondary outcomes were time to discharge from hospital and, in patients not receiving mechanical ventilation at randomisation, subsequent receipt of invasive mechanical ventilation (including extra-corporal membrane oxygenation) or death. Prespecified, subsidiary clinical outcomes included receipt of ventilation, time to successful cessation of invasive mechanical ventilation (defined as removal of invasive mechanical ventilation within, and survival to, 28 days), and use of renal dialysis or haemofiltration.

Prespecified safety outcomes were transfusion related adverse events at 72 h following randomisation (worsening respiratory status, suspected transfusion reaction, fever, hypotension, haemolysis, and thrombotic events), cause-specific mortality, and major cardiac arrhythmia. Information on serious adverse reactions to convalescent plasma was collected in an expedited fashion via the existing NHS Serious Hazards of Transfusion haemovigilence scheme.

**Statistical analysis**
In accordance with the statistical analysis plan, an intention-to-treat comparison was done between patients in the convalescent plasma group and those in the usual care group for whom convalescent plasma was both available and suitable as a treatment. For the primary outcome of 28-day mortality, the log-rank observed minus expected statistic and its variance were used both to test
were randomly assigned to receive tocilizumab with 552 randomly assigned to receive usual care alone.

randomisation to tocilizumab versus usual care in patients with hypoxia and C-reactive protein ≥75 mg/L was

5763 patients with completed follow-up at time of analysis received convalescent plasma. §A second

5795 patients with completed follow-up at time of analysis received convalescent plasma. ¶17 of

†Reasons for exclusion are not mutually exclusive. ‡Patients in the group are not included in the analyses of this

*Number recruited overall during period that patients could be recruited into convalescent plasma comparison.

16 287 patients recruited* 3360 excluded! 985 convalescent plasma unavailable 2784 unsuitable for convalescent plasma

11 558 randomised between convalescent plasma and usual care

1125 included in second randomisation||

23 withdrew consent

912 included in second randomisation||

25 withdrew consent

975 included in 28-day intention-to-treat analysis

5795 allocated convalescent plasma§

5763 allocated usual care¶

5763 included in 28-day intention-to-treat analysis

5763 included in 28-day intention-to-treat analysis

16 withdrew consent

1125 included in second randomisation||

1158 included in second randomisation

Figure 1: Trial profile

Additional sensitivity analyses included restricting analysis of the primary outcome to patients with a posi-
tive PCR test for SARS-CoV-2 and repeating subgroup analyses of the primary and secondary outcomes by

the null hypothesis of equal survival curves (ie, the log-rank test) and to calculate the one-step estimate of

the average mortality rate ratio. We used Kaplan-Meier survival curves to display cumulative mortality over the

28-day period. We used similar methods to analyse time to hospital discharge and successful cessation of invasive

mechanical ventilation, with patients who died in hospital right-censored on day 29. Median time to discharge

was derived from Kaplan-Meier estimates. For the prespecified, composite, secondary outcome of progression to invasive

mechanical ventilation or death within 28 days (in those not receiving invasive mechanical ventilation at ran-
donisation) and the subsidiary clinical outcomes of receipt of ventilation and use of haemodialysis or

haemofiltration, the precise dates were not available so the risk ratio was estimated instead.

Prespecified analyses of the primary outcome were done in seven subgroups defined by characteristics at

randomisation: age, sex, ethnicity, respiratory support received, days since symptom onset, use of systemic
corticosteroids, and presence of anti-SARS-CoV-2 antibody. Observed effects within these subgroup
categories were compared using a χ² test. Subgroup analyses according to these baseline characteristics
were also done for the secondary outcomes. Post-hoc exploratory analyses of the primary outcome included
examination by days since symptom onset, using four subcategories rather than the two that were prespecified,
and level of respiratory support by subdividing the oxygen only group into three subcategories. In late
2020, a new SARS-CoV-2 variant, named B.1.1.7, with multiple substitutions in the receptor binding domain
of the spike glycoprotein emerged in southeast England and rapidly grew to become the dominant virus variant
throughout the UK. 36 Convalescent plasma from individuals infected before the emergence of B.1.1.7 show a modest reduction in ability to neutralise B.1.1.7 compared with earlier SARS-CoV-2 virus variants. 37

The clinical significance of this reduced in-vitro neutralisation is not known. To assess if there was evidence of a difference in the effectiveness of con-

valescent plasma before and after the emergence of B.1.1.7, an additional post-hoc exploratory analysis was
done of the primary outcome comparing effects in patients randomly assigned before Dec 1, 2020, with
those randomly assigned from Dec 1, 2020, onwards. 38

Additional sensitivity analyses included restricting analysis of the primary outcome to patients with a posi-
tive PCR test for SARS-CoV-2 and repeating subgroup analyses of the primary and secondary outcomes by

presence of anti-SARS-CoV-2 antibody after adjustment for age. Age adjustment was done because in seronegative
patients those assigned to the convalescent plasma group were slightly younger than those assigned to the usual

care group, whereas in seropositive patients those assigned to the convalescent plasma group were slightly
older than those assigned to the usual care group. A final prespecified exploratory analysis estimated whether
the effect of allocation to convalescent plasma varied depending on whether the patient was simultaneously
allocated azithromycin (the only other treatment that has both already reported its results and to which substantial
numbers of patients could have been assigned at the same time as they were randomly assigned to receive
convalescent plasma or usual care).

Estimates of rate and risk ratios are shown with 95% CIs. All p values are two-sided and are shown
without adjustment for multiple testing. The full database is held by the trial team who pooled the data
from trial sites and did the analyses at the Nuffield Department of Population Health, University of Oxford.

For the primary outcome of 28-day mortality, the results from RECOVERY were subsequently included in
a meta-analysis of results from all previous randomised trials of convalescent plasma versus usual care in
patients with COVID-19. For each trial, we compared the observed number of deaths among patients allocated
convalescent plasma with the expected number if all
that the trial should enrol sufficient patients to provide at least 90% power to a two-sided p value of 0.01 to detect a proportional reduction in 28-day mortality of a fifth in patients with and, separately, without detectable SARS-CoV-2 antibodies at randomisation (appendix p 34).

On Jan 7, 2021, the independent data monitoring committee did a routine review of the data and recommended that the chief investigators pause recruitment to the convalescent plasma comparison in those patients receiving invasive mechanical ventilation (including extracorporeal membrane oxygenation) at the time of randomisation. At the same time, the committee recommended that recruitment to the convalescent plasma comparison continue for all other eligible patients.

On Jan 14, 2021, the data monitoring committee did another routine review of the data and notified the chief investigators that there was no convincing evidence that continued recruitment would provide conclusive proof of worthwhile mortality benefit, either overall or in any prespecified subgroup. The committee recommended that recruitment to the convalescent plasma portion of the study should cease and follow-up be completed. Enrolment of patients to the convalescent plasma comparison was closed on Jan 15, 2021, and the preliminary result for the primary outcome was made public. The trial is registered with ISRCTN, 50189673, and ClinicalTrials.gov, NCT04381936.

Table 1: Baseline characteristics
Role of the funding source
The funders of the trial had no role in trial design, data collection, data analysis, data interpretation, or writing of the report.

Results
Between May 28, 2020, and Jan 15, 2021, 16 287 patients enrolled into the RECOVERY trial were eligible to receive convalescent plasma (figure 1). 1569 (12%) were randomly assigned to the REGN-COV-2 group and are not included in the analyses reported here. Of the remaining 11 558 patients, 5795 (50%) were randomly assigned to the convalescent plasma group and 5763 (50%) to the usual care group. The mean age of the patients was 63·5 (SD 14·7) years, and the median time from symptom onset to randomisation was 9 days (IQR 6–12; table 1; appendix p 51). At randomisation, 617 (5%) of 11 558 patients were receiving invasive mechanical ventilation, 10 044 (87%) were receiving oxygen only (with or without non-invasive respiratory support), and 897 (8%) were receiving no oxygen therapy (appendix p 51). 10 681 (92%) of 11 558 patients were receiving corticosteroids at time of randomisation. By chance, a slightly lower proportion of men were randomly assigned to the convalescent plasma group than the usual care group, so Cox regression analyses adjusted for sex are provided.
Articles

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5030 (96%) of 5217 patients had their first unit of
plasma by the transfusion laboratory was known,
For patients in whom the time of issue of convalescent
5763 patients received two units, 644 (11%) received one
and seronegative patients (642 [32%] of 2016 patients
in the usual care group; rate ratio 0·62, 95% CI 0·24–1·62)
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in the usual care group; rate ratio 0·60 (0·22–1·58)
subtotals or totals of (O−E) and of V yield inverse-variance weighted averages of the ln rate
eratio values. †For balance, controls in the 2:1 studies count twice in the control totals and subtotals, but do not count twice when calculating their O−E or V values.
Baseline serology result were available for 9564 (83%)
of 11 558 patients, of whom 3676 (38%) were SARS-CoV-2
antibody seronegative (appendix p 51). Patients were
more likely to be seronegative if they were older, female,
White, had shorter duration of symptoms, were receiving
less intensive respiratory support, or were SARS-CoV-2
RNA negative by PCR (appendix p 52). There was an
imbalance in the availability of a baseline serology
sample, with more missing samples in the usual care
group (table 1).
In the convalescent plasma group, 4657 (80%) of
5795 patients received two units, 644 (11%) received one
unit, and 494 (9%) received no units (appendix p 53).
Two (<1%) patients received both convalescent plasma
units from the same donor. In the usual care group, 17 (<1%) of 5763 patients received convalescent plasma.
For patients in whom the time of issue of convalescent
plasma by the transfusion laboratory was known, 5030 (96%) of 5217 patients had their first unit of
plasma issued within 36 h of randomisation. Use of
corticosteroids and remdesivir following randomisa
tion was similar between the two groups (appendix p 53).
Slightly fewer patients received tocilizumab or sarilumab
in the convalescent plasma group (447 [8%] of 5795) than
in the usual care group (589 [10%] of 5763 patients; appendix p 53).
Primary and secondary outcome data were known
for 99% of randomly assigned patients. There was no
significant difference in 28-day mortality between the
two groups: 1399 (24%) of 5795 patients died in
the convalescent plasma group and 1408 (24%) of
5763 patients died in the usual care group (rate ratio 1·00,
95% CI 0·93–1·07; p=0·95; figure 3). We observed
similar results across all subgroups with no good
evidence of heterogeneity of effect in either the
prespecified (figure 3) or the exploratory post-hoc
(appendix p 59) subgroup analyses (all p values
were >0·05). Results were similar in analyses restricted
to patients with a positive SARS-CoV-2 test (rate ratio 1·00,
95% CI 0·93–1·08; p=0·93) and there was no evidence
that the rate ratio differed depending on allocation to
azithromycin (p>0·1). Although 28-day mortality was
higher in patients who were seronegative at randomisation, the proportional effect of allocation to
convalescent plasma on 28-day mortality was similar in
seropositive patients (575 [19%] of 3078 patients in the
convalescent plasma group vs 501 [18%] of 2810 patients
in the usual care group; rate ratio 1·06, 95% CI 0·94–1·19)
and seronegative patients (642 [32%] of 2016 patients
in the convalescent plasma group vs 558 [34%] of
1660 patients in the usual care group; rate ratio 0·96,
95% CI 0·85–1·07; figure 3; appendix p 59).
Figure 4: Meta-analysis of mortality in RECOVERY and other trials
O−E—observed–expected. Var—variance. RR—rate ratio. *Log-rank O−E for RECOVERY. O−E from 2 × 2 contingency tables for the other trials. RR is calculated by taking
ln rate ratio to be (O−E)/V with normal variance 1/V, where V=Var (O−E). Subtotals or totals of (O−E) and of V yield inverse-variance weighted averages of the ln rate
ratio values. †For balance, controls in the 2:1 studies count twice in the control totals and subtotals, but do not count twice when calculating their O−E or V values.
Heterogeneity between RECOVERY and ten previous trials combined, χ₁²=2·7 (p=0·10).
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| (appendix p 57), which are almost identical to the main
results shown.

Baseline serology result were available for 9564 (83%)
of 11 558 patients, of whom 3676 (38%) were SARS-CoV-2
antibody seronegative (appendix p 51). Patients were
more likely to be seronegative if they were older, female,
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in the convalescent plasma group (447 [8%] of 5795) than
in the usual care group (589 [10%] of 5763 patients; appendix p 53).
Primary and secondary outcome data were known
for 99% of randomly assigned patients. There was no
significant difference in 28-day mortality between the
meta-analysis, the mortality rate ratio was 0.98 (95% CI 0.91–1.06; p=0.63; figure 4).

The median time to discharge was 12 days in the convalescent plasma group and 11 days in the usual care group (IQR 6 to >28 in both groups); patients in the convalescent plasma group had a similar probability of being discharged alive within 28 days compared with the usual care group (3832 [66%] of 5795 patients in the convalescent plasma group vs 3822 [66%] of 5763 patients in the usual care group; rate ratio 0.99, 95% CI 0.94 to 1.03; p=0.57; table 2). Of the patients who were not receiving invasive mechanical ventilation at baseline, the number of patients progressing to the prespecified composite secondary outcome of invasive mechanical ventilation or death was similar in the two groups (1568 [29%] of 5493 patients in the convalescent plasma group vs 1568 [29%] of 5448 patients in the usual care group; rate ratio 0.99, 95% CI 0.93 to 1.05; p=0.79; table 2). For both of these secondary outcomes, there was some evidence of heterogeneity by patient SARS-CoV-2 antibody test result, with slightly more favourable outcomes with convalescent plasma in patients who were seronegative at baseline compared with those who were seropositive (appendix pp 61–62). Because of slight age-imbalance between treatment groups for both seropositive and seronegative patients, an exploratory analysis was done that included adjustment for age, which marginally reduced the apparent heterogeneity (heterogeneity p=0.02 for both secondary outcomes after age adjustment). Results were consistent across all other prespecified subgroups of patients.

There were no significant differences in the prespecified subsidiary clinical outcomes of use of ventilation, successful cessation of invasive mechanical ventilation, or progression to use of renal replacement therapy (table 2), or in cause-specific mortality (appendix p 54).

Within the first 72 h after randomisation, severe allergic reactions were reported in 16 (<1%) of 5795 patients in the convalescent plasma group and two (<1%) of 5763 patients in the usual care group. The frequency of sudden worsening in respiratory status, temperature higher than 39°C or a 2°C or higher increase in temperature above baseline, sudden hypotension, clinical haemorrhage, and thrombotic events were broadly similar in the two groups (appendix p 55). We also observed no significant differences in the frequency of major cardiac arrhythmia (appendix p 55). 13 patients receiving convalescent plasma had reports submitted to the Serious Hazards of Transfusion haemovigilence scheme: nine patients with pulmonary reactions (none considered to be transfusion-related acute lung injury, including three deaths possibly related to transfusion), and four patients with serious febrile, allergic, or hypotensive reactions (all of whom recovered).

### Discussion

The results of this large, randomised trial show that convalescent plasma did not improve survival or other clinical outcomes in patients hospitalised with COVID-19. The results were consistent across subgroups of age, sex, ethnicity, duration of symptoms before randomisation, level of respiratory support received at randomisation, and use of corticosteroids. The results are consistent with the evidence from previously reported randomised trials of convalescent plasma for patients hospitalised with COVID-19, with no evidence of a survival benefit when these results are combined (figure 4).

It has been suggested that the benefits of convalescent plasma depend on the transfused neutralising titre, and that using plasma with lower titres could explain negative results from previous randomised trials. In RECOVERY, all convalescent plasma was supplied via the UK National Blood Services using standardised laboratory processing. Convalescent donors were chosen based on high anti-spike IgG concentrations, using an ELISA that has been shown to correlate well with neutralising antibody. We used a EUROIMMUN sample to cutoff ratio of 6.0 for plasma to qualify for use in this trial, which is substantially more than the 3.5 cutoff that the US FDA recognises as high titre. Nearly all participants received plasma from two different donors to increase the chance that at least one contained higher concentrations of neutralising antibodies.
The presence of anti-SARS-CoV-2 antibodies in recipients at the time of transfusion with convalescent plasma has also been cited as a possible reason for the absence of an observed effect. In this trial we found that 38% of patients were seronegative at randomisation, and, although they had a markedly higher 28-day mortality risk than patients who were seropositive at randomisation, we did not observe a significant survival benefit from convalescent plasma in these patients. Our results do not exclude the possibility of small improvements in the probability of successful discharge from hospital by day 28 or of progressing to invasive mechanical ventilation or death in seronegative patients who received convalescent plasma. However, the results of these secondary outcomes in one subgroup should be interpreted with caution given the multiple testing; additionally, when an age-adjusted analysis was done the apparent heterogeneity was slightly reduced.

It has also been suggested that antibody-based therapies could be most effective in the early stages of COVID-19, when viral replication dominates. We did not identify a benefit of convalescent plasma when patients were stratified by time since onset of illness in the main analysis or in an exploratory analysis, which subdivided participants on the basis of illness onset. Of note, we did not identify a mortality benefit in the subgroup of patients allocated to convalescent plasma 4 days or less from illness onset, which by itself comprised more patients than the total number of patients enrolled in all other convalescent plasma trials combined. However, RECOVERY only included patients admitted to hospital; therefore, the trial does not address whether convalescent plasma has any benefit if given early after SARS-CoV-2 infection and before the onset of significant disease. That question has not yet been robustly tested in sufficiently large randomised controlled trials.

Following random assignment to receive convalescent plasma, patients with hypoxia and a raised C-reactive protein (≥75mg/L) were eligible for a second random assignment to receive usual care or usual care plus tocilizumab. Although a slightly lower proportion of patients allocated convalescent plasma (8%) subsequently received tocilizumab than patients allocated usual care (10%; appendix p 33), and although tocilizumab itself reduces 28-day mortality by around 15%, this difference is far too small to have had any material effect on our estimate of the effect of convalescent plasma on mortality (estimated 0–1% difference in 28 day mortality). SARS-CoV-2 is an RNA virus with antigenic variability. The efficacy of convalescent plasma is likely to depend on the match between the strain-specific transfused anti-SARS-CoV-2 antibodies in donor plasma and the infecting virus variant in the recipient. In December, 2020, a new SARS-CoV-2 variant (B.1.1.7) was detected in the southeast and east of England, with an earliest date of detection in September, 2020. B.1.1.7 spread rapidly to become the dominant SARS-CoV-2 variant, in most regions of the UK, by January, 2021. Although B.1.1.7 has changes in the spike glycoprotein that could theoretically modify antigenicity, only modest reductions in neutralisation by convalescent plasma have been reported. Consistent with this, we did not identify any evidence of a differential effect of convalescent plasma before and after the emergence of B.1.1.7 in the UK (appendix p 59).

During an epidemic caused by a novel virus, convalescent plasma is an appealing treatment because it might be available within weeks of the outbreak, long before other targeted therapies are available. Consequently, convalescent plasma has been widely used for COVID-19 outside of clinical trials but, until now, there has been insufficient evidence from randomised trials to reliably assess its safety and efficacy. In RECOVERY, the largest clinical trial of convalescent plasma for any infectious indication, we did not find evidence that high-titre convalescent plasma improved survival or other prespecified clinical outcomes in patients hospitalised with COVID-19. Whether convalescent plasma would benefit other patient groups is unknown and would need to be evaluated in other, adequately powered, randomised clinical trials.

Contributors
This manuscript was initially drafted by the PWH and MJL, further developed by the Writing Committee, and approved by all members of the trial steering committee. PWH and MJL vouch for the data and analyses, and for the fidelity of this report to the trial protocol and data analysis plan. PWH, LE, LP, MM, JKB, LCC, SNF, TJ, KJ, WSL, AM, KR, FJ, DJR, RH, and MJL designed the trial and trial protocol. MM, AR, GP-A, NJB, TG, DZ, ST, NNA, AU, JW, GJ, TB, SS, RH, the Data Linkage team at the RECOVERY Coordinating Centre, and the health records and local clinical centre staff listed in the appendix collected the data. ES, NS, and JRE did the statistical analysis. LE, DJR, and the blood and transfusion service staff listed in the appendix coordinated the collection and supply of convalescent plasma. All authors contributed to data interpretation and critical review and revision of the manuscript. PWH and MJL had access to the trial data and had final responsibility for the decision to submit for publication.

Writing Committee (on behalf of the RECOVERY Collaborative Group)

Data Monitoring Committee
Peter Sandercock, Janet Darbyshire, David DeMets, Robert Fowler, David Lallos, Ian Roberts (until December 2020), Mohammed Munavvar (from January 2021), Janet Wittes.

Declaration of interests
We declare no competing interests.

Data sharing
The protocol, consent form, statistical analysis plan, definition and derivation of clinical characteristics and outcomes, training materials, regulatory documents, and other relevant trial materials are available online. As described in the protocol, the trial steering committee will facilitate the use of the trial data and approval will not be unreasonably withheld. Deidentified participant data will be made available to bona fide researchers registered with an appropriate institution within...
3 months of publication. However, the steering committee will need to be satisfied that any proposed publication is of high quality, honour the commitments made to the trial patients in the consent documentation and ethical approvals, and is compliant with relevant legal and regulatory requirements (eg, relating to data protection and privacy). The steering committee will have the right to review and comment on any draft manuscripts before publication. Data will be made available in line with the policy and procedures available online. Those wishing to request access should complete the form available online and emailed to data.access@ndph.ox.ac.uk.

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