

Tocilizumab for COVID-19

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Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomised, controlled, open-label, platform trial

Running title: Tocilizumab for COVID-19

RECOVERY Collaborative Group*

*The writing committee and trial steering committee are listed at the end of this manuscript and a complete list of collaborators in the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial is provided in the Supplementary Appendix.

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23 SUMMARY

24 **Background:** Tocilizumab is a monoclonal antibody that binds to the receptor for
25 interleukin (IL)-6, reducing inflammation, and is commonly used to treat rheumatoid
26 arthritis. We evaluated the safety and efficacy of tocilizumab in adult patients admitted to
27 hospital with COVID-19 with evidence of both hypoxia and systemic inflammation.

28 **Methods:** This randomised, controlled, open-label, platform trial (Randomised Evaluation
29 of COVID-19 Therapy [RECOVERY]), is assessing several possible treatments in
30 patients hospitalised with COVID-19 in the UK. Those trial participants with hypoxia
31 (oxygen saturation <92% on air or requiring oxygen therapy) and evidence of systemic
32 inflammation (C-reactive protein [CRP] ≥ 75 mg/L) were eligible for randomisation to usual
33 standard of care alone versus usual standard of care plus tocilizumab at a dose of 400
34 mg to 800 mg (depending on weight) given intravenously. A second dose could be given
35 12 to 24 hours later if the patient's condition had not improved. The primary outcome was
36 28-day mortality, assessed in the intention-to-treat population. The trial is registered with
37 ISRCTN (50189673) and clinicaltrials.gov (NCT04381936).

38 **Findings:** Between 23 April 2020 and 24 January 2021, 4116 adults were included in the
39 assessment of tocilizumab, including 562 (14%) patients receiving invasive mechanical
40 ventilation, 1686 (41%) receiving non-invasive respiratory support, and 1868 (45%)
41 receiving no respiratory support other than oxygen. Median CRP was 143 [IQR 107-204]
42 mg/L and 3385 (82%) patients were receiving systemic corticosteroids at randomisation.
43 Overall, 596 (29%) of the 2022 patients allocated tocilizumab and 694 (33%) of the 2094
44 patients allocated to usual care died within 28 days (rate ratio 0.86; 95% confidence

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45 interval [CI] 0.77-0.96; $p=0.007$). Consistent results were seen in all pre-specified
46 subgroups of patients. In particular, a clear mortality benefit was seen in those receiving
47 systemic corticosteroids. Patients allocated to tocilizumab were more likely to be
48 discharged from hospital alive within 28 days (54% vs. 47%; rate ratio 1.22; 95% CI 1.12-
49 1.34; $p<0.0001$). Among those not receiving invasive mechanical ventilation at baseline,
50 patients allocated tocilizumab were less likely to reach the composite endpoint of invasive
51 mechanical ventilation or death (33% vs. 38%; risk ratio 0.85; 95% CI 0.78-0.93;
52 $p=0.0005$).

53 **Interpretation:** In hospitalised COVID-19 patients with hypoxia and systemic
54 inflammation, tocilizumab improved survival and other clinical outcomes. These benefits
55 were seen regardless of the level of respiratory support and were additional to the benefits
56 of systemic corticosteroids.

57 **Funding:** UK Research and Innovation (Medical Research Council) and National Institute
58 of Health Research (Grant ref: MC_PC_19056).

59 **Keywords:** COVID-19, tocilizumab, clinical trial.

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61 INTRODUCTION

62 The majority of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
63 infections are either asymptomatic or result in only mild disease.¹ However, a substantial
64 proportion of infected individuals develop a respiratory illness requiring hospital care,
65 which can progress to critical illness with hypoxic respiratory failure requiring prolonged
66 ventilatory support. Among COVID-19 patients admitted to UK hospitals in Spring 2020,
67 the case fatality rate was over 26%, and was in excess of 37% in patients requiring
68 invasive mechanical ventilation.²

69 Hypoxic respiratory failure in patients with COVID-19 is associated with evidence of
70 systemic inflammation, including release of pro-inflammatory cytokines, such as
71 interleukin (IL)-1, IL-6 and TNF α , and elevated levels of D-dimers, ferritin, and C-reactive
72 protein (CRP).^{3,4} The host immune response is thought to play a key role in driving an
73 acute inflammatory pneumonic process with diffuse alveolar damage, myeloid cell
74 infiltrates, and microvascular thrombosis.⁵ The beneficial effects of dexamethasone and
75 other corticosteroids in COVID-19 patients with hypoxic lung damage suggest that other,
76 more specific immunomodulatory agents may provide additional improvements in clinical
77 outcomes.^{6,7}

78 Tocilizumab is a recombinant humanised anti-IL-6 receptor monoclonal antibody that
79 inhibits the binding of IL-6 to both membrane and soluble IL-6 receptors, blocking IL-6
80 signalling and reducing inflammation. Tocilizumab is licensed in the UK as an intravenous
81 treatment for patients with rheumatoid arthritis and for people with chimeric antigen
82 receptor T cell-induced severe or life-threatening cytokine release syndrome.

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83 Randomised trials of tocilizumab in COVID-19 have so far shown mixed results for 28-
84 day mortality: six small trials reported no benefit while the somewhat larger REMAP-CAP
85 trial reported a benefit in patients requiring organ support.⁸⁻¹⁴ Here we report the results
86 of a large randomised controlled trial of tocilizumab in adult patients hospitalised with
87 severe COVID-19 characterised by hypoxia and significant inflammation.

88

89 **METHODS**

90 **Study design and participants**

91 The Randomised Evaluation of COVID-19 therapy (RECOVERY) trial is an investigator-
92 initiated, individually randomised, controlled, open-label, platform trial to evaluate the
93 effects of potential treatments in patients hospitalised with COVID-19. Details of the trial
94 design and results for other possible treatments have been published previously.^{6,15-17}
95 The trial is being conducted in acute National Health Service (NHS) hospitals in the UK,
96 supported by the National Institute for Health Research Clinical Research Network. The
97 trial is coordinated by the Nuffield Department of Population Health at University of Oxford
98 (Oxford, UK), the trial sponsor. The trial is conducted in accordance with the principles of
99 the International Conference on Harmonisation–Good Clinical Practice guidelines and
100 approved by the UK Medicines and Healthcare products Regulatory Agency (MHRA) and
101 the Cambridge East Research Ethics Committee (ref: 20/EE/0101). The protocol,
102 statistical analysis plan, and additional information are available on the study website
103 www.recoverytrial.net. This report is limited to adult patients. The randomised
104 assessment of tocilizumab in children under 18 years old is ongoing.

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105 Patients admitted to hospital were eligible for the study if they had clinically suspected or
106 laboratory confirmed SARS-CoV-2 infection and no medical history that might, in the
107 opinion of the attending clinician, put the patient at significant risk if they were to
108 participate in the trial. Written informed consent was obtained from all patients, or their
109 legal representative if they were too unwell or unable to provide consent.

110 **Randomisation and masking**

111 Data were collected at study entry using a web-based case report form that included
112 demographics and major comorbidities (appendix p 32). All eligible and consenting
113 patients received usual standard of care and underwent an initial (main) randomisation
114 comprising up to 3 parts in a factorial design (appendix p 29): part 1, no additional
115 treatment vs. either dexamethasone, lopinavir-ritonavir, hydroxychloroquine,
116 azithromycin, or colchicine; part 2, no additional treatment vs. either convalescent plasma
117 or REGN-COV2 (a combination of two monoclonal antibodies directed against SARS-
118 CoV-2 spike protein); and part 3, no additional treatment vs. aspirin. Over time, treatment
119 arms were added to and removed from the protocol (appendix p 26), and not all
120 treatments were available at every hospital. Similarly, not all treatments were suitable for
121 some patients (e.g. due to comorbid conditions or concomitant medication). In any of
122 these cases, randomisation was between fewer arms.

123 Up to 21 days after the main randomisation and regardless of treatment allocation,
124 RECOVERY trial participants with clinical evidence of progressive COVID-19 (defined as
125 oxygen saturation <92% on room air or receiving oxygen therapy, and CRP \geq 75 mg/L)
126 could be considered for randomisation to tocilizumab vs. usual care alone. Baseline data

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127 collected for this second randomisation included level of respiratory support, markers of
128 progressive COVID-19 (including oxygen saturation, CRP, ferritin, creatinine), suitability
129 for the study treatment, and treatment availability at the site (appendix p 34). For some
130 patients, tocilizumab was unavailable at the hospital at the time of enrolment or was
131 considered by the managing physician to be either definitely indicated or definitely
132 contraindicated. In such cases, the patients were not eligible for the tocilizumab
133 randomisation. Patients with known hypersensitivity to tocilizumab, evidence of active
134 tuberculosis infection or clear evidence of active bacterial, fungal, viral, or other infection
135 (besides COVID-19) were not eligible for randomisation to tocilizumab.

136 Patients who were eligible for randomisation to tocilizumab were assigned to either usual
137 standard of care or usual standard of care plus tocilizumab in a 1:1 ratio using web-based
138 simple (unstratified) randomisation with allocation concealed until after randomisation.
139 Patients allocated to tocilizumab were to receive tocilizumab as a single intravenous
140 infusion over 60 minutes. The dose of tocilizumab was determined by body weight (800
141 mg if weight >90kg; 600 mg if weight >65 and ≤90 kg; 400 mg if weight >40 and ≤65 kg;
142 and 8mg/kg if weight ≤40 kg). A second dose could be given 12 to 24 hours later if, in the
143 opinion of the attending clinician, the patient's condition had not improved. Allocated
144 treatment was prescribed by the managing doctor. Roche Products Ltd (UK) supported
145 the trial through provision of tocilizumab. Participants and local study staff were not
146 masked to the allocated treatment. The steering committee, investigators, and all others
147 involved in the trial were masked to the outcome data during the trial.

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149 **Procedures**

150 A single online follow-up form was completed when participants were discharged, had
151 died or at 28 days after the initial randomisation, whichever occurred earliest (appendix p
152 36-41). Information was recorded on adherence to allocated study treatment, receipt of
153 other COVID-19 treatments, duration of admission, receipt of respiratory or renal support,
154 and vital status (including cause of death). In addition, routine healthcare and registry
155 data were obtained for the full follow-up period, including information on vital status (with
156 date and cause of death), discharge from hospital, receipt of respiratory support, or renal
157 replacement therapy.

158 **Outcomes**

159 Outcomes were assessed at 28 days after randomisation to tocilizumab vs. usual care
160 alone, with further analyses specified at 6 months. The primary outcome was all-cause
161 mortality. Secondary outcomes were time to discharge alive from hospital, and, among
162 patients not receiving invasive mechanical ventilation at randomisation, receipt of invasive
163 mechanical ventilation (including extra-corporeal membrane oxygenation) or death.
164 Prespecified subsidiary clinical outcomes were use of non-invasive respiratory support
165 (defined as high flow nasal oxygen, continuous positive airway pressure, or non-invasive
166 ventilation), time to successful cessation of invasive mechanical ventilation (defined as
167 cessation of invasive mechanical ventilation within, and survival to, 28 days), and use of
168 renal dialysis or haemofiltration. Prespecified safety outcomes included cause-specific
169 mortality and major cardiac arrhythmia. Information on suspected serious adverse
170 reactions was collected in an expedited fashion to comply with regulatory requirements.

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171 **Statistical Analysis**

172 In accordance with the statistical analysis plan (version 2.1 appendix pp 93-117), an
173 intention-to-treat comparison was conducted between patients who entered the
174 randomised comparison of tocilizumab vs. usual care. For the primary outcome of 28-day
175 mortality, the log-rank observed minus expected statistic and its variance were used to
176 test the null hypothesis of equal survival curves (i.e., the log-rank test) and to calculate
177 the one-step estimate of the average mortality rate ratio. We constructed Kaplan-Meier
178 survival curves to display cumulative mortality over the 28-day period. For this preliminary
179 report, information on the primary outcome is available for 92% of randomised patients.
180 Those patients who had not been followed for 28 days and were not known to have died
181 by the time of the data cut for this preliminary analysis (8 February 2021) were either
182 censored on 8 February 2021 or, if they had already been discharged alive, were right-
183 censored for mortality at day 29 (that is, in the absence of any information to the contrary
184 they were assumed to have survived 28 days). [Note: This censoring rule will not be
185 necessary when all patients have completed the 28 day follow-up period on 25 February
186 2021.] We used the same method to analyse time to hospital discharge and successful
187 cessation of invasive mechanical ventilation, with patients who died in hospital right-
188 censored on day 29. For the pre-specified composite secondary outcome of invasive
189 mechanical ventilation or death within 28 days (among those not receiving invasive
190 mechanical ventilation at randomisation) and the subsidiary clinical outcomes of receipt
191 of ventilation and receipt of haemodialysis or haemofiltration, the precise dates were not
192 available and so the risk ratio was estimated instead.

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193 Prespecified analyses of the primary outcome were performed in subgroups defined by
194 six characteristics at the time of randomisation: age, sex, ethnicity, level of respiratory
195 support, days since symptom onset, and use of systemic corticosteroids (including
196 dexamethasone). Observed effects within subgroup categories were compared using a
197 chi-squared test for heterogeneity or trend, in accordance with the prespecified analysis
198 plan.

199 Estimates of rate and risk ratios are shown with 95% confidence intervals. All p-values
200 are 2-sided and are shown without adjustment for multiple testing. The full database is
201 held by the study team which collected the data from study sites and performed the
202 analyses at the Nuffield Department of Population Health, University of Oxford (Oxford,
203 UK).

204 Prior to commencement of the randomisation to tocilizumab vs. usual care, the trial
205 steering committee determined that if 28-day mortality in the usual care group was
206 above 25% then recruitment of around 4000 patients to this comparison would provide
207 90% power at two-sided $P=0.01$ to detect a proportional reduction in 28-day mortality of
208 one-fifth. Consequently, Roche Products Ltd provided sufficient treatment for 2000
209 patients to receive tocilizumab. The trial steering committee, masked to the results,
210 closed recruitment to the tocilizumab comparison at the end of January 24, 2021 as
211 over 4000 patients had been randomised.

212 Analyses were performed using SAS version 9.4 and R version 3.4. The trial is registered
213 with ISRCTN (50189673) and clinicaltrials.gov (NCT04381936).

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215 **Role of the funding source**

216 Neither the funders of the study nor Roche Products Ltd had any role in study design,
217 data collection, data analysis, data interpretation, or writing of the report. Roche Products
218 Ltd supported the study through the supply of tocilizumab and reviewed the draft
219 publication for factual accuracy relating to tocilizumab. The corresponding authors had
220 full access to all the data in the study and had final responsibility for the decision to submit
221 for publication.

222

223 **RESULTS**

224 Between 14 April 2020 and 24 January 2021, 4116 (19%) of 21550 patients enrolled into
225 the RECOVERY trial at one of the 131 sites in the UK participating in the tocilizumab
226 comparison were eligible for randomisation. 2022 patients were randomly allocated to
227 tocilizumab and 2094 were randomly allocated to usual care. The mean age of these
228 participants was 63.6 years (SD 13.7). At randomisation, 562 (14%) patients were
229 receiving invasive mechanical ventilation, 1686 (41%) were receiving non-invasive
230 respiratory support (including high-flow nasal oxygen, continuous positive airway
231 pressure, and non-invasive ventilation), and 1868 (45%) were receiving no respiratory
232 support other than simple oxygen therapy (9 of these patients were reportedly not
233 receiving oxygen at randomisation) (table 1). Median CRP was 143 [IQR 107-204] mg/L.
234 82% of patients were reported to be receiving corticosteroids at randomisation (and 97%
235 of the patients enrolled since the announcement of the dexamethasone result from
236 RECOVERY in June 2021).

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237 The follow-up form was completed for 1602 (79%) of 2022 randomised patients in the
238 tocilizumab group and 1664 (79%) of 2094 patients in the usual care group. [Follow-up
239 forms are expected for >95% of participants by the time of the final analyses.] Among
240 patients with a completed follow-up form, 1333 (83%) allocated to tocilizumab and 44
241 (3%) of those allocated to usual care received at least one dose of tocilizumab (or
242 sarilumab, another IL-6 antagonist; figure 1; webtable 1). 461 (29%) patients in the
243 tocilizumab group and 10 (<1%) in the usual care group received more than 1 dose of
244 tocilizumab (or sarilumab). Use of other treatments for COVID-19 during the 28 days after
245 randomisation was similar among patients allocated tocilizumab and among those
246 allocated usual care (webtable 1).

247 Allocation to tocilizumab was associated with a significant reduction in the primary
248 outcome of 28-day mortality compared with usual care alone (596 [29%] of 2022 patients
249 in the tocilizumab group vs. 694 (33%) of 2094 patients in the usual care group; rate ratio
250 0.86; 95% confidence interval [CI], 0.77 to 0.96; $p=0.007$; figure 2a). In an exploratory
251 analysis restricted to the 3858 (94%) patients with a positive SARS-CoV-2 test result, the
252 result was similar (rate ratio 0.87, 95% CI 0.78 to 0.98; $p=0.02$).

253 Allocation to tocilizumab was associated with a greater probability of discharge from
254 hospital alive within 28 days (54% vs. 47%; rate ratio 1.22, 95% CI 1.12 to 1.34, $p<0.0001$;
255 figure 2b and table 2). Among those not on invasive mechanical ventilation at baseline,
256 allocation to tocilizumab was associated with a reduction in the risk of progressing to the
257 pre-specified composite secondary outcome of invasive mechanical ventilation or death
258 when compare to usual care alone (33% vs. 38%, risk ratio 0.85, 95% CI 0.78 to 0.93,
259 $p=0.0005$; table 2).

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260 We observed similar results across all pre-specified sub-groups (figure 3 and webfigures
261 2 and 3), including the level of respiratory support at randomisation (figure 3). Given the
262 number of hypothesis tests conducted, the suggestion of a larger proportional mortality
263 reduction among those receiving a corticosteroid compared with those not [interaction
264 $p=0.01$] may reflect the play of chance. An exploratory analysis showed that the effects
265 of tocilizumab on 28-day mortality were similar for those randomised ≤ 2 or > 2 days since
266 hospitalisation (interaction $p=0.86$).

267 In pre-specified subsidiary analyses, we found no significant effect of tocilizumab on
268 subsequent receipt of non-invasive respiratory support or invasive mechanical ventilation
269 among those on no respiratory support at randomisation (table 2, webfigure 1). Nor was
270 there a significant effect on the rate of successful cessation of invasive mechanical
271 ventilation among those on invasive mechanical ventilation at randomisation. However,
272 allocation to tocilizumab reduced the use of haemodialysis or haemofiltration (5% vs. 7%,
273 risk ratio 0.75, 95% CI 0.59 to 0.96, $p=0.02$; table 2). Preliminary information on cause-
274 specific mortality shows no evidence of excess deaths from other infections (webtable 2).
275 We observed no significant differences in the frequency of new cardiac arrhythmias
276 (webtable 3). There were three reports of serious adverse reactions believed to be related
277 to tocilizumab: one each of otitis externa, *Staphylococcus aureus* bacteraemia, and lung
278 abscess, all of which resolved with standard treatment.

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281 **DISCUSSION**

282 The results of this large, randomised trial indicate that tocilizumab is an effective
283 treatment for hospitalised COVID-19 patients who have hypoxia and evidence of
284 inflammation (CRP ≥ 75 mg/L). Treatment with tocilizumab improved survival and the
285 chances of discharge from hospital alive by 28 days, and reduced the chances of
286 progressing to require invasive mechanical ventilation. These benefits were consistent
287 across all patient groups studied, including those receiving invasive mechanical
288 ventilation, non-invasive respiratory support, or no respiratory support other than simple
289 oxygen. The benefits of tocilizumab were clearly seen among those also receiving
290 treatment with a systemic corticosteroid such as dexamethasone. There was also a
291 significant reduction in the need for haemodialysis or haemofiltration. Although we did not
292 see any effect on the duration of invasive mechanical ventilation, only 185 patients had
293 such ventilation successfully removed within the first 28 days, so power to detect any
294 benefit was low.

295 Since mid-2020, seven randomised controlled trials of tocilizumab for the treatment of
296 COVID-19 have reported. These include six small trials (fewer than 100 deaths in each)
297 and the somewhat larger REMAP-CAP trial, which recruited critically ill patients with
298 COVID-19, over 99% of whom required non-invasive respiratory support or invasive
299 mechanical ventilation.⁸⁻¹⁴ Taken together, these previous trials did not show a significant
300 mortality benefit for treatment with tocilizumab (death rate ratio 0.91, 95% CI 0.72-1.14,
301 figure 4). The RECOVERY trial contains over three times as many deaths as all the
302 previous trials combined. When all 8 trials are considered together, allocation to

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303 tocilizumab is associated with a 13% proportional reduction in 28-day mortality (death
304 rate ratio 0.87, 95% CI 0.79-0.96, $p=0.005$, figure 4).

305 These benefits are in addition to those previously reported for corticosteroids, which is
306 now usual standard of care for COVID-19 patients requiring treatment with oxygen.^{6,18}

307 Our data suggest that in COVID-19 patients who are hypoxic and have evidence of
308 systematic inflammation, treatment with a combination of a systemic corticosteroid plus
309 tocilizumab would be expected to reduce mortality by about one-third for patients
310 receiving simple oxygen and nearly one-half for those receiving invasive mechanical
311 ventilation.

312 Previous trials have provided weak evidence that tocilizumab may shorten time to
313 discharge or reduce progression to invasive mechanical ventilation or death.^{10,14} Our
314 results show that in a broad spectrum of patients, tocilizumab increases the chances of
315 being discharged alive within 28 days and reduces the chance of progression to receiving
316 invasive mechanical ventilation. As with the mortality benefit, these effects are consistent
317 regardless of the level of respiratory support at the time of enrolment.

318 Strengths of this trial included that it was randomised, had a large sample size, and
319 included patients requiring various levels of respiratory support (from simple oxygen
320 through to invasive mechanical ventilation). There are some limitations: For this
321 preliminary report, information on the primary outcome is available for 92% of patients.

322 This should increase to >99% by early March when all patients have passed the 28-day
323 follow-up period. Following random assignment, 17% of patients in the tocilizumab group
324 did not receive this treatment. The reasons for this were not recorded. The size of the

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325 effects of tocilizumab reported in this paper are therefore an underestimate of the true
326 effects of actually using the treatment. Hospital stay is very long for many of these patients
327 (median >28 days); the pre-planned analyses at 6 months will provide additional
328 information on the full effects of tocilizumab on clinical outcomes.

329 The RECOVERY results support the use of tocilizumab, but other IL-6 antagonists are
330 available. Although the effects of sarilumab in REMAP-CAP were similar to tocilizumab,
331 only 48 participants received sarilumab.⁸ Two larger trials of sarilumab have completed
332 but have not reported any results (NCT044327388, NTC044315298). Publication of
333 results from those trials is now essential to assess whether alternative IL-6 antagonists
334 to tocilizumab are effective.

335 Guidelines on the use of IL-6 antagonists for patients with severe COVID-19 vary. For
336 example the US National Institutes for Health conclusion is that there are insufficient data
337 to recommend either for or against the use of tocilizumab or sarilumab, a view shared by
338 some commentators.^{19,20} By contrast, interim guidance in the NHS states that IL-6
339 antagonists should be considered for patients within 24 hours of starting non-invasive
340 respiratory support or invasive mechanical ventilation.²¹ Our results show that the benefits
341 of tocilizumab extend to a broader group of patients receiving oxygen with or without other
342 forms of respiratory support, and that those benefits include a reduction in the need for
343 invasive mechanical ventilation and other organ support such as renal replacement
344 therapy. Since complicating bacterial infections are infrequent in the early hospitalisation
345 period of COVID-19, this recognised concern in relation to the use of tocilizumab would
346 be lessened with earlier use.²²

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347 Based upon the ISARIC4C database, approximately 49% of hospitalised COVID-19
348 patients in the UK would meet our inclusion criteria and hence would benefit from
349 tocilizumab (personal communication, ISARIC4C Investigators). CRP was chosen as the
350 biomarker for inflammation in this study since it is widely used and affordable worldwide,
351 it is correlated with serum IL-6 levels, and early clinical studies of COVID-19 had reported
352 it to be associated with severity and prognosis, with a value of >50 mg/L associated with
353 severe disease and a level of around 75 mg/L distinguishing fatal from non-fatal cases.²³⁻
354 ²⁸ Whether hypoxic patients with a CRP <75 mg/L could benefit from tocilizumab is
355 unknown. Further work is also needed to consider the health economic benefits of
356 tocilizumab and related IL-6 inhibitors in terms of both patient outcomes and usage of
357 healthcare resources (duration of hospital stay, and frequency of invasive mechanical
358 ventilation and renal replacement therapy).

359 The RECOVERY trial has demonstrated that for patients hospitalized with severe COVID,
360 treatment with tocilizumab reduces mortality, increases the chances of successful
361 hospital discharge, and reduces the chances of requiring invasive mechanical ventilation.
362 These benefits are additional to those previously reported for dexamethasone. These
363 findings require an update to clinical guidelines and efforts to increase the global
364 availability and affordability of tocilizumab.

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366 **Contributors**

367 This manuscript was initially drafted by the PWH and MJL, further developed by the
368 Writing Committee, and approved by all members of the trial steering committee. PWH
369 and MJL vouch for the data and analyses, and for the fidelity of this report to the study
370 protocol and data analysis plan. PWH, MM, JKB, LCC, SNF, TJ, KJ, WSL, AM, KR, EJ,
371 RH, and MJL designed the trial and study protocol. MM, AR, G P-A, CB, RS, ICT, VJ, AA,
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373 Centre, Health Records, and Local Clinical Centre staff listed in the appendix collected
374 the data. ES, NS, and JRE verified the data and did the statistical analysis. All authors
375 contributed to data interpretation and critical review and revision of the manuscript. PWH
376 and MJL had access to the study data and had final responsibility for the decision to
377 submit for publication.

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431 **Data Monitoring Committee**

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434 **Declaration of interests**

435 The authors have no conflict of interest or financial relationships relevant to the submitted
436 work to disclose. No form of payment was given to anyone to produce the manuscript. All
437 authors have completed and submitted the ICMJE Form for Disclosure of Potential
438 Conflicts of Interest. The Nuffield Department of Population Health at the University of
439 Oxford has a staff policy of not accepting honoraria or consultancy fees directly or
440 indirectly from industry (see [https://www.ndph.ox.ac.uk/files/about/ndph-independence-](https://www.ndph.ox.ac.uk/files/about/ndph-independence-of-research-policy-jun-20.pdf)
441 [of-research-policy-jun-20.pdf](https://www.ndph.ox.ac.uk/files/about/ndph-independence-of-research-policy-jun-20.pdf)).

442 **Data sharing**

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443 The protocol, consent form, statistical analysis plan, definition & derivation of clinical
444 characteristics & outcomes, training materials, regulatory documents, and other relevant
445 study materials are available online at www.recoverytrial.net. As described in the protocol,
446 the trial steering committee will facilitate the use of the study data and approval will not
447 be unreasonably withheld. Deidentified participant data will be made available to bona
448 fide researchers registered with an appropriate institution within 3 months of publication.
449 However, the steering committee will need to be satisfied that any proposed publication
450 is of high quality, honours the commitments made to the study participants in the consent
451 documentation and ethical approvals, and is compliant with relevant legal and regulatory
452 requirements (e.g. relating to data protection and privacy). The steering committee will
453 have the right to review and comment on any draft manuscripts prior to publication. Data
454 will be made available in line with the policy and procedures described at:
455 <https://www.ndph.ox.ac.uk/data-access>. Those wishing to request access should
456 complete the form at
457 https://www.ndph.ox.ac.uk/files/about/data_access_enquiry_form_13_6_2019.docx
458 and e-mailed to: data.access@ndph.ox.ac.uk

459

460 **Acknowledgements**

461 Above all, we would like to thank the thousands of patients who participated in this study.
462 We would also like to thank the many doctors, nurses, pharmacists, other allied health
463 professionals, and research administrators at 176 NHS hospital organisations across the
464 whole of the UK, supported by staff at the National Institute of Health Research (NIHR)
465 Clinical Research Network, NHS DigiTrials, Public Health England, Department of Health

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466 & Social Care, the Intensive Care National Audit & Research Centre, Public Health
467 Scotland, National Records Service of Scotland, the Secure Anonymised Information
468 Linkage (SAIL) at University of Swansea, and the NHS in England, Scotland, Wales and
469 Northern Ireland.

470 The RECOVERY trial is supported by a grant to the University of Oxford from UK
471 Research and Innovation/NIHR (Grant reference: MC_PC_19056) and by core funding
472 provided by NIHR Oxford Biomedical Research Centre, Wellcome, the Bill and Melinda
473 Gates Foundation, the Department for International Development, Health Data Research
474 UK, the Medical Research Council Population Health Research Unit, the NIHR Health
475 Protection Research Unit in Emerging and Zoonotic Infections, and NIHR Clinical Trials
476 Unit Support Funding. TJ is supported by a grant from UK Medical Research Council
477 (MC_UU_0002/14) and an NIHR Senior Research Fellowship (NIHR-SRF-2015-08-001).
478 WSL is supported by core funding provided by NIHR Nottingham Biomedical Research
479 Centre. Abbvie contributed some supplies of lopinavir-ritonavir for use in this study.
480 Roche Products Ltd supported the trial through the provision of tocilizumab. REGEN-
481 COV2 was provided for this study by Regeneron.

482 The views expressed in this publication are those of the authors and not necessarily those
483 of the NHS, the National Institute for Health Research, the Department of Health and
484 Social Care, or Roche Products Limited.

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Tocilizumab for COVID-19

486 References

- 487 1. Verity R, Okell LC, Dorigatti I, et al. Estimates of the severity of coronavirus
488 disease 2019: a model-based analysis. *Lancet Infect Dis* 2020; **20**(6): 669-77.
- 489 2. Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in
490 hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol:
491 prospective observational cohort study. *Bmj* 2020; **369**: m1985.
- 492 3. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99
493 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study.
494 *Lancet* 2020.
- 495 4. Del Valle DM, Kim-Schulze S, Huang HH, et al. An inflammatory cytokine
496 signature predicts COVID-19 severity and survival. *Nat Med* 2020; **26**(10): 1636-43.
- 497 5. Dorward DA, Russell CD, Um IH, et al. Tissue-Specific Immunopathology in Fatal
498 COVID-19. *Am J Respir Crit Care Med* 2021; **203**(2): 192-201.
- 499 6. Horby P, Lim WS, Emberson JR, et al. Dexamethasone in Hospitalized Patients
500 with Covid-19 - Preliminary Report. *N Engl J Med* 2020.
- 501 7. WHO Rapid Evidence Appraisal for COVID-19 Therapies Working Group, Sterne
502 JAC, Murthy S, et al. Association Between Administration of Systemic Corticosteroids
503 and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. *JAMA* 2020;
504 **324**(13): 1330-41.
- 505 8. Gordon AC, Mouncey PR, Al-Beidh F, et al. Interleukin-6 Receptor Antagonists in
506 Critically Ill Patients with Covid-19 – Preliminary report. *medRxiv* 2021:
507 2021.01.07.21249390.
- 508 9. Veiga VC, Prats JAGG, Farias DLC, et al. Effect of tocilizumab on clinical
509 outcomes at 15 days in patients with severe or critical coronavirus disease 2019:
510 randomised controlled trial. *BMJ* 2021; **372**: n84.
- 511 10. Rosas I, Bräu N, Waters M, et al. Tocilizumab in Hospitalized Patients With
512 COVID-19 Pneumonia. *medRxiv* 2020: 2020.08.27.20183442.
- 513 11. Hermine O, Mariette X, Tharaux PL, et al. Effect of Tocilizumab vs Usual Care in
514 Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia: A
515 Randomized Clinical Trial. *JAMA Intern Med* 2021; **181**(1): 32-40.
- 516 12. Salvarani C, Dolci G, Massari M, et al. Effect of Tocilizumab vs Standard Care on
517 Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia: A Randomized
518 Clinical Trial. *JAMA Intern Med* 2021; **181**(1): 24-31.
- 519 13. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of Tocilizumab in Patients
520 Hospitalized with Covid-19. *N Engl J Med* 2020; **383**(24): 2333-44.

Tocilizumab for COVID-19

- 521 14. Salama C, Han J, Yau L, et al. Tocilizumab in Patients Hospitalized with Covid-
522 19 Pneumonia. *N Engl J Med* 2021; **384**(1): 20-30.
- 523 15. Recovery Collaborative Group, Horby P, Mafham M, et al. Effect of
524 Hydroxychloroquine in Hospitalized Patients with Covid-19. *N Engl J Med* 2020;
525 **383**(21): 2030-40.
- 526 16. Recovery Collaborative Group. Azithromycin in patients admitted to hospital with
527 COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*
528 2021.
- 529 17. Recovery Collaborative Group, Horby PW, Mafham M, et al. Lopinavir-ritonavir in
530 patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled,
531 open-label, platform trial. *Lancet* 2020; **396**(10259): 1345-52.
- 532 18. Sterne JAC, Diaz J, Villar J, et al. Corticosteroid therapy for critically ill patients
533 with COVID-19: A structured summary of a study protocol for a prospective meta-
534 analysis of randomized trials. *Trials* 2020; **21**(1): 734.
- 535 19. National Institutes of Health. The COVID-19 Treatment Guidelines Panel's
536 Statement on the Use of Tocilizumab (and Other Interleukin-6 Inhibitors) for the
537 Treatment of COVID-19. 2021.
538 <https://www.covid19treatmentguidelines.nih.gov/statement-on-tocilizumab/> (accessed
539 10/02/2021).
- 540 20. McCreary EK, Meyer NJ. Covid-19 controversies: the tocilizumab chapter. *BMJ*
541 2021; **372**: n244.
- 542 21. MHRA. Interleukin-6 inhibitors (tocilizumab and sarilumab) for critically ill patients
543 with COVID-19 pneumonia (adults). 2021.
544 <https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103138>
545 (accessed 10/02/2021).
- 546 22. Baskaran V, Lawrence H, Lansbury L, et al. Co-infection in critically ill patients
547 with COVID-19: An observational cohort study from England. *medRxiv* 2020:
548 2020.10.27.20219097.
- 549 23. Escadafal C, Incardona S, Fernandez-Carballo BL, Dittrich S. The good and the
550 bad: using C reactive protein to distinguish bacterial from non-bacterial infection among
551 febrile patients in low-resource settings. *BMJ Glob Health* 2020; **5**(5).
- 552 24. Oberhoffer M, Karzai W, Meier-Hellmann A, Bogel D, Fassbinder J, Reinhart K.
553 Sensitivity and specificity of various markers of inflammation for the prediction of tumor
554 necrosis factor-alpha and interleukin-6 in patients with sepsis. *Crit Care Med* 1999;
555 **27**(9): 1814-8.
- 556 25. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease
557 2019 in China. *N Engl J Med* 2020; **382**(18): 1708-20.

Tocilizumab for COVID-19

- 558 26. Qin C, Zhou L, Hu Z, et al. Dysregulation of Immune Response in Patients With
559 Coronavirus 2019 (COVID-19) in Wuhan, China. *Clin Infect Dis* 2020; **71**(15): 762-8.
- 560 27. Wang L, He W, Yu X, et al. Coronavirus disease 2019 in elderly patients:
561 Characteristics and prognostic factors based on 4-week follow-up. *J Infect* 2020; **80**(6):
562 639-45.
- 563 28. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to
564 COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive*
565 *Care Med* 2020.
566
- 567

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568 **Figures**

569

570 **Figure 1: Trial profile - Flow of participants through the RECOVERY trial**

571

572 **Figure 2: Effect of allocation to tocilizumab on (a) 28-day mortality and (b)**

573 **discharge from hospital alive within 28 days of randomisation**

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575 **Figure 3: Effect of allocation to tocilizumab on 28-day mortality by pre-specified**

576 **characteristics at randomisation**

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578 **Figure 4: Meta-analysis of mortality in randomised controlled trials of tocilizumab**

579 **in patients hospitalised with COVID-19**

580

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581 **Table 1: Baseline characteristics by randomised allocation**

	Tocilizumab (n=2022)	Usual care (n=2094)
Mean (SD) Age, years	63.3 (13.7)	63.9 (13.6)
≥18 to <70	1332 (66%)	1354 (65%)
≥70 to <80	477 (24%)	480 (23%)
≥80	213 (11%)	260 (12%)
Sex		
Male	1335 (66%)	1437 (69%)
Female*	687 (34%)	657 (31%)
Ethnicity		
White	1356 (67%)	1426 (68%)
Black, Asian, or Minority Ethnic	341 (17%)	357 (17%)
Unknown	325 (16%)	311 (15%)
Number of days since symptom onset	9 (7-13)	10 (7-14)
Number of days since hospitalisation	2 (1-5)	2 (1-5)
Oxygen saturation, %	94 (92-96)	94 (91-95)
Respiratory support at second randomisation		
No ventilator support†	935 (46%)	933 (45%)
Non-invasive ventilation‡	819 (41%)	867 (41%)
Invasive mechanical ventilation§	268 (13%)	294 (14%)
Biochemistry at second randomisation		
Latest C-reactive protein, mg/L	143 (107-203)	144 (106-205)
Ferritin, ng/mL	947 (497-1599)	944 (507-1533)
Creatinine, umol/L	77 (62-98)	77 (62-100)
Previous diseases		
Diabetes	569 (28%)	600 (29%)
Heart disease	435 (22%)	497 (24%)
Chronic lung disease	473 (23%)	484 (23%)
Tuberculosis	3 (<1%)	5 (<1%)
HIV	7 (<1%)	8 (<1%)
Severe liver disease¶	14 (<1%)	10 (<1%)
Severe kidney impairment	118 (6%)	99 (5%)
Any of the above	1100 (54%)	1163 (56%)
SARS-Cov-2 test result		
Positive	1891 (94%)	1967 (94%)
Negative	68 (3%)	66 (3%)
Test result not yet known	63 (3%)	61 (3%)
First randomisation§		
Number of days since first randomisation	0 (0-1)	0 (0-1)

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	Tocilizumab (n=2022)	Usual care (n=2094)
Part A allocation		
Usual care	839 (41%)	869 (41%)
Lopinavir/ritonavir	51 (3%)	64 (3%)
Dexamethasone	49 (2%)	45 (2%)
Hydroxychloroquine	37 (2%)	38 (2%)
Azithromycin	197 (10%)	177 (8%)
Use of systemic corticosteroids[^]		
Yes	1664 (82%)	1721 (82%)
No	357 (18%)	367 (18%)
Unknown	1 (<1%)	6 (<1%)

Data are mean (SD), n(%), or median (IQR). Information on sex, ethnicity, and SARS-CoV-2 test result were recorded on the main randomisation form when patients first entered the study. All other information was recorded on the second randomisation form (when patients were randomly assigned to tocilizumab vs. usual care alone). * includes 3 pregnant women. † Includes 9 patients not receiving any oxygen and 1859 patients receiving low-flow oxygen. ‡ includes patients receiving high-flow nasal oxygen, continuous positive airway pressure, or other non-invasive ventilation). § Includes patients receiving invasive mechanical ventilation or extra-corporeal membranous oxygenation. ¶ Defined as requiring ongoing specialist care. || Defined as estimated glomerular filtration rate <30 mL/min/1.73m² § 2631 and 1615 participants were randomised into parts B and C of the first randomisation respectively. ^Information on use of corticosteroids was collected from 18 June 2020 onwards following announcement of the results of the dexamethasone comparison from the RECOVERY trial. Participants undergoing first randomisation prior to this date (and who were not allocated to dexamethasone) are assumed not to be receiving systemic corticosteroids.

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Table 2: Effect of allocation to tocilizumab on main study outcomes

	Treatment allocation		RR (95% CI)	p value
	Tocilizumab (n=2022)	Usual care (n=2094)		
Primary outcome				
Total: 28-day mortality	596 (29%)	694 (33%)	0.86 (0.77-0.96)	0.0066
Secondary outcomes				
Median time to being discharged alive, days	20	>28		
Discharged alive from hospital within 28 days	1093 (54%)	990 (47%)	1.22 (1.12-1.34)	<0.0001
Receipt of invasive mechanical ventilation or death*	571/1754 (33%)	687/1800 (38%)	0.85 (0.78-0.93)	0.0005
Invasive mechanical ventilation	215/1754 (12%)	273/1800 (15%)	0.81 (0.68-0.95)	0.01
Death	471/1754 (27%)	552/1800 (31%)	0.88 (0.79-0.97)	0.01
Subsidiary clinical outcomes				
Receipt of ventilation†	233/935 (25%)	242/933 (26%)	0.96 (0.82-1.12)	0.61
Non-invasive ventilation	222/935 (24%)	223/933 (24%)	0.99 (0.84-1.17)	0.94
Invasive mechanical ventilation	45/935 (5%)	63/933 (7%)	0.71 (0.49-1.03)	0.07
Successful cessation of invasive mechanical ventilation‡	91/268 (34%)	94/294 (32%)	1.07 (0.80-1.43)	0.64
Use of haemodialysis or haemofiltration§	103/2003 (5%)	142/2075 (7%)	0.75 (0.59-0.96)	0.02

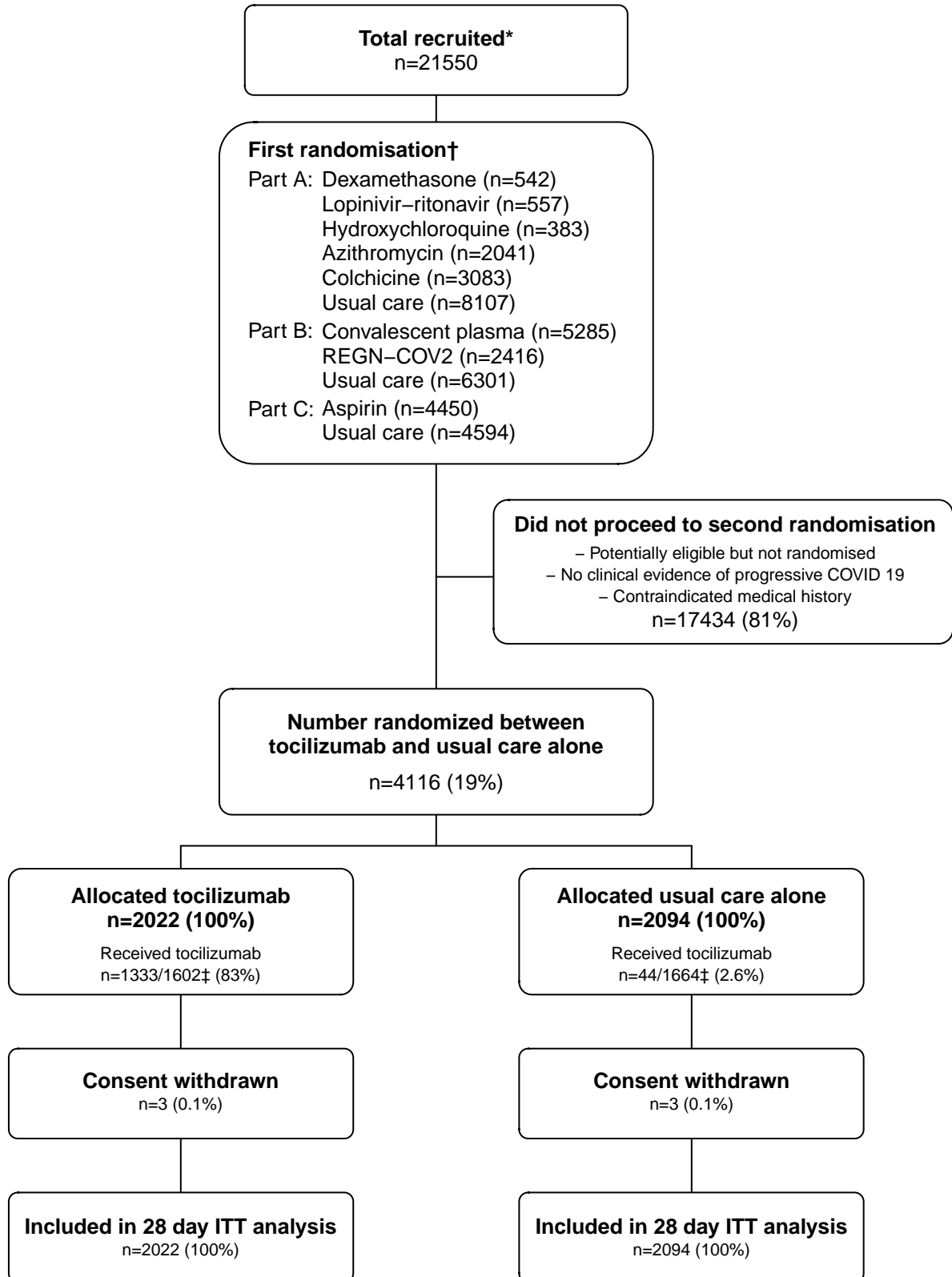
Data are n(%), n/N (%), or median (interquartile range). RR=rate ratio for the outcomes of 28-day mortality, hospital discharge and successful cessation of invasive mechanical ventilation, and risk ratio for other outcomes. * Analyses include only those on no ventilator support or non-invasive ventilation at second randomisation. † Analyses include only those on no ventilator support at second randomisation. ‡ Analyses restricted to those on invasive mechanical ventilation at second randomisation. § Analyses exclude those on haemodialysis or haemofiltration at second randomisation.

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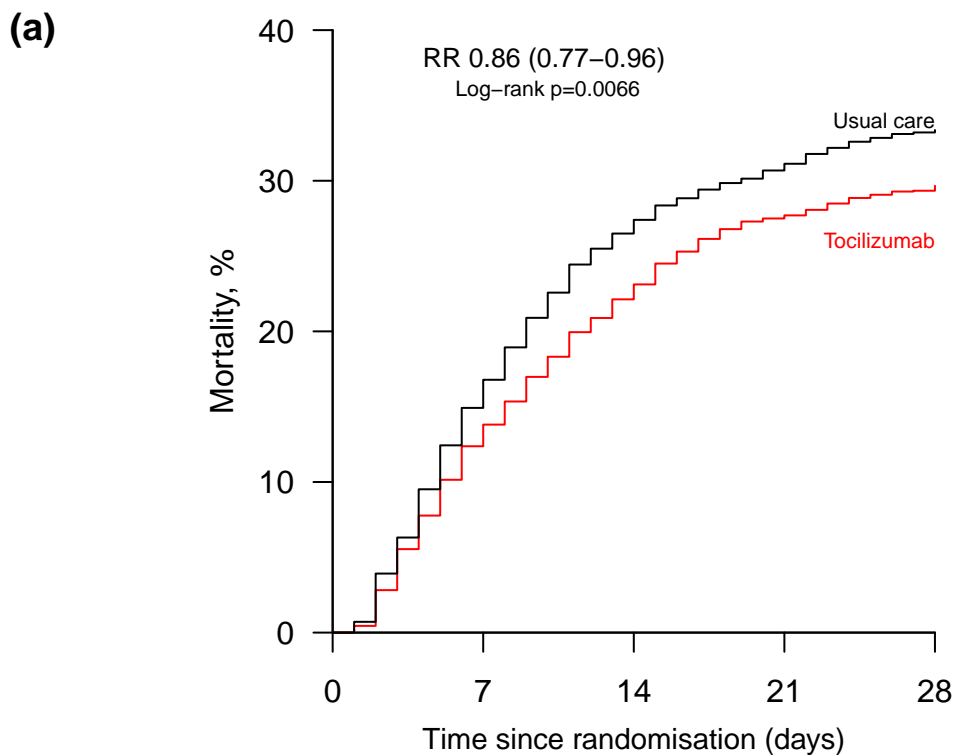
Figure 1: Trial profile – Flow of participants through the RECOVERY trial

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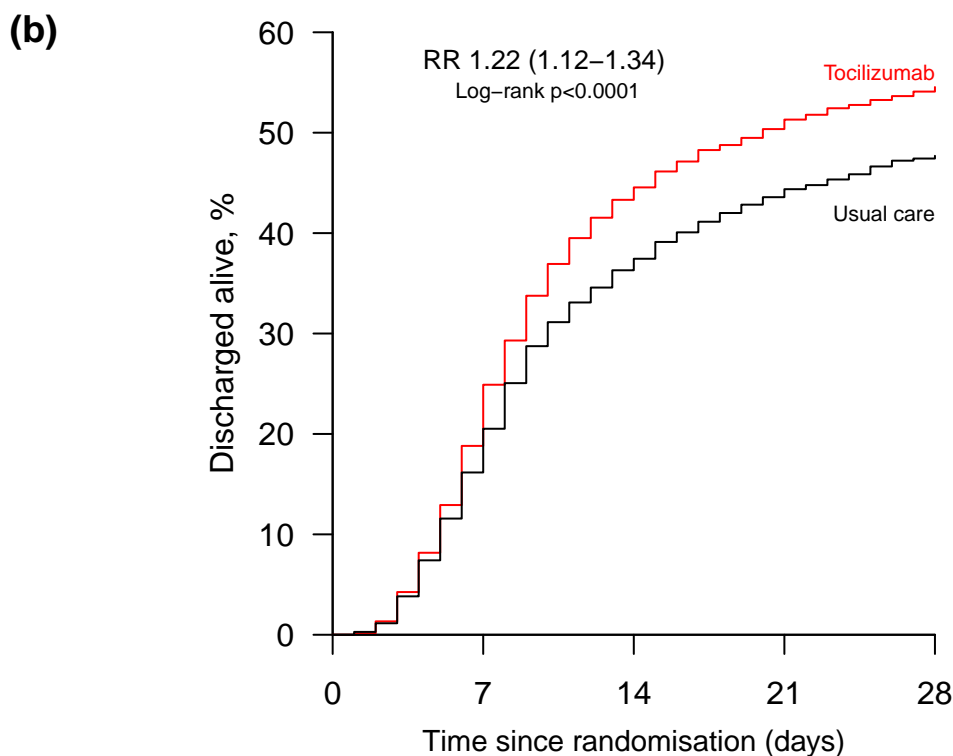


ITT=intention to treat. *Number of adult patients recruited at a site activated for the tocilizumab comparison. †The first randomisation comprised up to 3 factorial elements such that an eligible patient could be entered into between 1 and 3 randomised comparisons, depending on the then current protocol, the patients suitability for particular treatments, and the availability of the treatment at the site. ‡ 1602/2022 (79%) patients of those allocated to tocilizumab and 1664/2094 (79%) of those allocated to usual care had a completed follow-up form at time of analysis.

Figure 2: Effect of allocation to tocilizumab on (a) 28-day mortality and (b) discharge from hospital alive within 28 days of randomisation

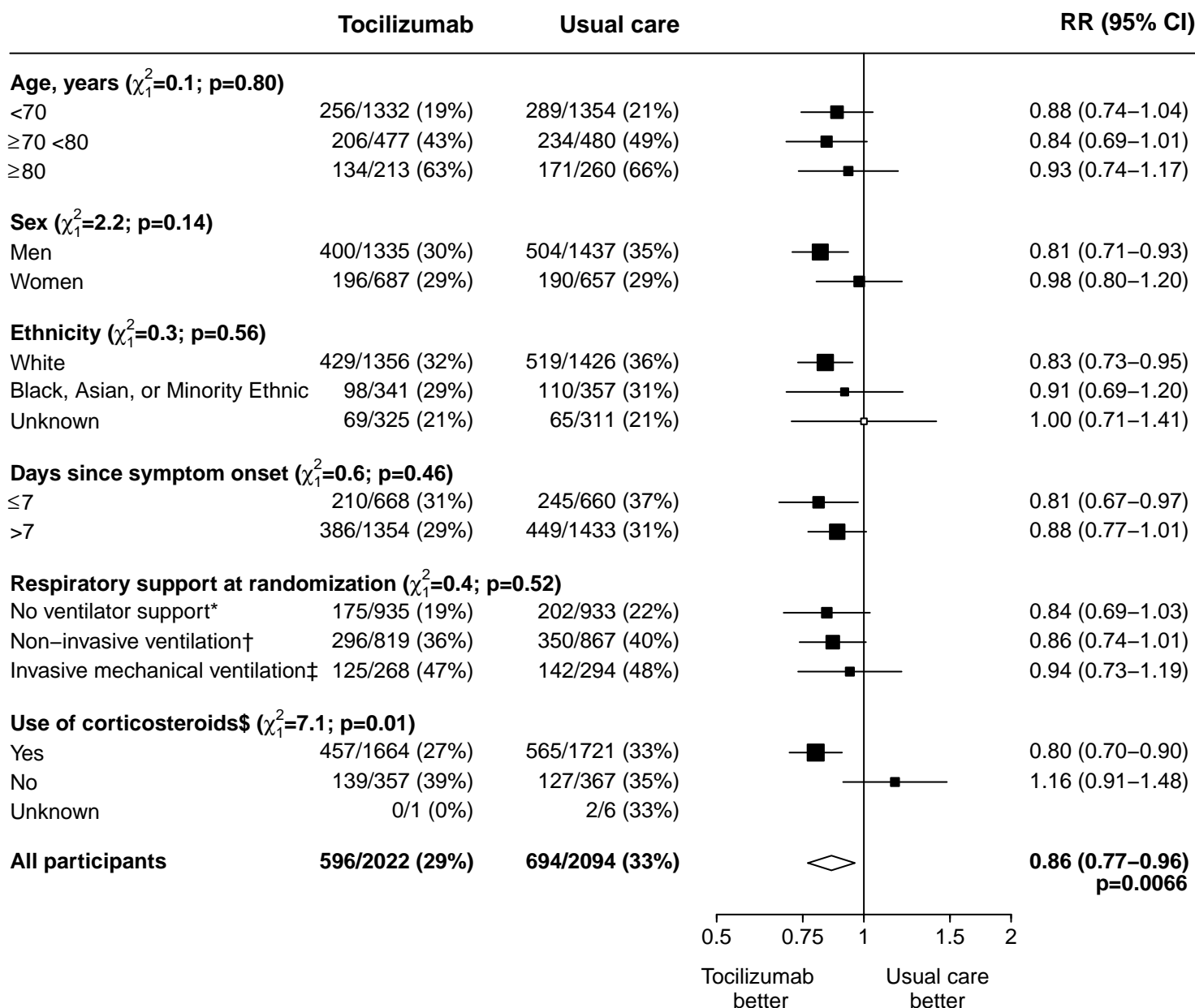


Number at risk	0	7	14	21	28
Active	2022	1741	1553	1386	1284
Control	2094	1740	1518	1372	1250



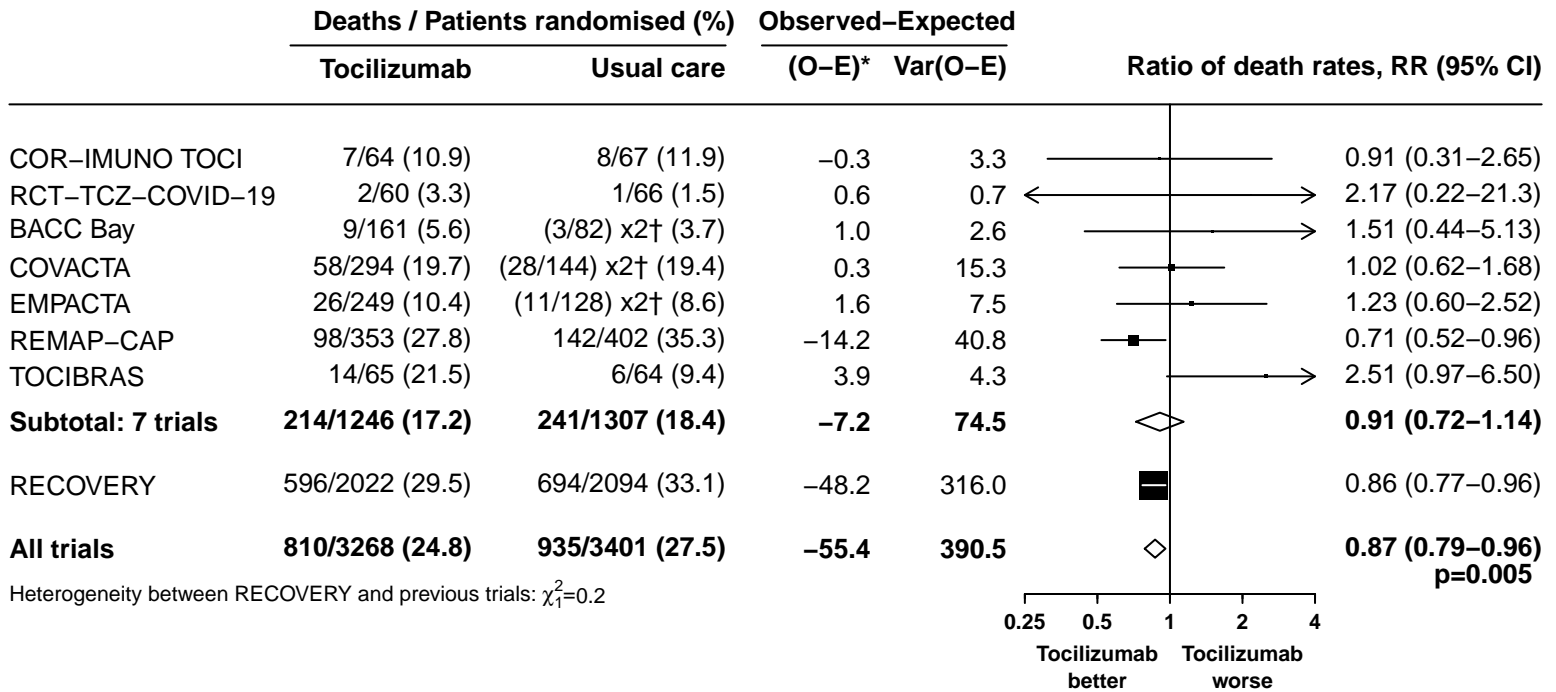
Number at risk	0	7	14	21	28
Active	2022	1517	1120	911	787
Control	2094	1662	1308	1096	954

Figure 3: Effect of allocation to tocilizumab on 28-day mortality by baseline characteristics



Subgroup-specific rate ratio estimates are represented by squares (with areas of the squares proportional to the amount of statistical information) and the lines through them correspond to the 95% CIs. The ethnicity and days since onset subgroups exclude those with missing data, but these patients are included in the overall summary diamond. * Includes 9 patients not receiving any oxygen and 1859 patients receiving simple oxygen only. † Includes patients receiving high-flow nasal oxygen, continuous positive airway pressure ventilation, other non-invasive ventilation. ‡ Includes patients receiving invasive mechanical ventilation and extra-corporeal membranous oxygenation. \$ Information on use of corticosteroids was collected from 18 June 2020 onwards following announcement of the results of the dexamethasone comparison from the RECOVERY trial. Participants undergoing first randomisation prior to this date (and who were not allocated to dexamethasone) are assumed not to be receiving systemic corticosteroids.

Figure 4: Tocilizumab vs usual care in patients hospitalised with COVID – Meta-analysis of mortality in RECOVERY and other trials



* Log-rank O-E for RECOVERY, O-E from 2x2 tables for the other trials. RR is calculated by taking $\ln RR$ to be $(O-E)/V$ with Normal variance $1/V$. Subtotals or totals of (O-E) and of V yield inverse-variance-weighted averages of the $\ln RR$ values.

† For balance, controls in the 2:1 studies count twice in the control totals and subtotals.