

Hydroxychloroquine for COVID-19 – Preliminary Report

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Effect of Hydroxychloroquine in Hospitalized Patients with COVID-19: Preliminary results from a multi-centre, randomized, controlled trial.

Running title: Hydroxychloroquine for COVID-19 – Preliminary Report

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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27 **ABSTRACT**

28 **Background:** Hydroxychloroquine and chloroquine have been proposed as treatments for
29 coronavirus disease 2019 (COVID-19) on the basis of in vitro activity, uncontrolled data, and
30 small randomized studies.

31 **Methods:** The Randomised Evaluation of COVID-19 therapy (RECOVERY) trial is a
32 randomized, controlled, open-label, platform trial comparing a range of possible treatments with
33 usual care in patients hospitalized with COVID-19. We report the preliminary results for the
34 comparison of hydroxychloroquine vs. usual care alone. The primary outcome was 28-day
35 mortality.

36 **Results:** 1561 patients randomly allocated to receive hydroxychloroquine were compared with
37 3155 patients concurrently allocated to usual care. Overall, 418 (26.8%) patients allocated
38 hydroxychloroquine and 788 (25.0%) patients allocated usual care died within 28 days (rate
39 ratio 1.09; 95% confidence interval [CI] 0.96 to 1.23; P=0.18). Consistent results were seen in
40 all pre-specified subgroups of patients. Patients allocated to hydroxychloroquine were less likely
41 to be discharged from hospital alive within 28 days (60.3% vs. 62.8%; rate ratio 0.92; 95% CI
42 0.85-0.99) and those not on invasive mechanical ventilation at baseline were more likely to
43 reach the composite endpoint of invasive mechanical ventilation or death (29.8% vs. 26.5%; risk
44 ratio 1.12; 95% CI 1.01-1.25). There was no excess of new major cardiac arrhythmia.

45 **Conclusions:** In patients hospitalized with COVID-19, hydroxychloroquine was not associated
46 with reductions in 28-day mortality but was associated with an increased length of hospital stay
47 and increased risk of progressing to invasive mechanical ventilation or death.

48 **Funding:** Medical Research Council and NIHR (Grant ref: MC_PC_19056).

49 **Trial registrations:** The trial is registered with ISRCTN (50189673) and clinicaltrials.gov
50 (NCT04381936).

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51 **Keywords:** COVID-19, hydroxychloroquine, clinical trial.

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53 **INTRODUCTION**

54 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus
55 disease 2019 (COVID-19), emerged in China in late 2019 from a zoonotic source.¹ The majority
56 of COVID-19 infections are either asymptomatic or result in only mild disease. However, a
57 substantial proportion of infected individuals develop a respiratory illness requiring hospital
58 care,² which can progress to critical illness with hypoxemic respiratory failure requiring
59 prolonged ventilatory support.³⁻⁶ Amongst COVID-19 patients admitted to UK hospitals, the case
60 fatality rate is around 26%, and is over 37% in patients requiring invasive mechanical
61 ventilation.⁷

62 Hydroxychloroquine and chloroquine, 4-aminoquinoline drugs developed over 70 years ago and
63 used to treat malaria and rheumatological conditions, have been proposed as treatments for
64 COVID-19. Chloroquine has in vitro activity against a variety of viruses, including SARS-CoV-2
65 and the related SARS-CoV-1.⁸⁻¹³ The exact mechanism of antiviral action is uncertain but these
66 drugs increase the pH of endosomes that the virus uses for cell entry and also interfere with the
67 glycosylation of the cellular receptor of SARS-CoV, angiotensin-converting enzyme 2 (ACE2),
68 and associated gangliosides.^{10,14} The 4-aminoquinoline concentrations required to inhibit SARS-
69 CoV-2 replication in vitro are relatively high by comparison with the free plasma concentrations
70 observed in the prevention and treatment of malaria.¹⁵ These drugs are generally well tolerated,
71 inexpensive and widely available. Following oral administration they are rapidly absorbed, even
72 in severely ill patients. If active, therapeutic hydroxychloroquine concentrations could be
73 expected in the human lung shortly after an initial loading dose.

74 Small pre-clinical studies have reported that hydroxychloroquine prophylaxis or treatment had
75 no beneficial effect of clinical disease or viral replication.¹⁶ Clinical benefit and antiviral effect
76 from the administration of these drugs alone or in combination with azithromycin to patients with
77 COVID-19 infections has been reported in some observational studies¹⁷⁻²¹ but not in others.²²⁻²⁴

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78 A few small controlled trials of hydroxychloroquine and chloroquine for the treatment of COVID-
79 19 infection have been inconclusive.²⁵⁻²⁸ Here we report preliminary results of the effects of a
80 randomized controlled trial of hydroxychloroquine in patients hospitalized with COVID-19.

81

82 **METHODS**

83 **Trial design and participants**

84 The RECOVERY trial is an investigator-initiated, individually randomized, controlled, open-label,
85 platform trial to evaluate the effects of potential treatments in patients hospitalized with COVID-
86 19. The trial is conducted at 176 hospitals in the United Kingdom (see Supplementary
87 Appendix), supported by the National Institute for Health Research Clinical Research Network.
88 The trial is coordinated by the Nuffield Department of Population Health at University of Oxford,
89 the trial sponsor. Although the hydroxychloroquine, dexamethasone, and lopinavir-ritonavir arms
90 have now been stopped, the trial continues to study the effects of azithromycin, tocilizumab, and
91 convalescent plasma (and other treatments may be studied in the future).

92 Hospitalized patients were eligible for the study if they had clinically suspected or laboratory
93 confirmed SARS-CoV-2 infection and no medical history that might, in the opinion of the
94 attending clinician, put the patient at significant risk if they were to participate in the trial. Initially,
95 recruitment was limited to patients aged at least 18 years but from 9 May 2020, the age limit
96 was removed. Patients with known prolonged electrocardiograph QTc interval were ineligible for
97 the hydroxychloroquine arm. Co-administration with medications that prolong the QT interval
98 was not an absolute contraindication but attending clinicians were advised to check the QT
99 interval by performing an electrocardiogram.

100 Written informed consent was obtained from all patients or from a legal representative if they
101 were too unwell or unable to provide consent. The trial was conducted in accordance with the

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102 principles of the International Conference on Harmonization–Good Clinical Practice guidelines
103 and approved by the UK Medicines and Healthcare Products Regulatory Agency (MHRA) and
104 the Cambridge East Research Ethics Committee (ref: 20/EE/0101). The protocol and statistical
105 analysis plan are available in the Supplementary Appendix and on the study website
106 www.recoverytrial.net.

107 **Randomization**

108 Baseline data collected using a web-based case report form included demographics, level of
109 respiratory support, major comorbidities, the suitability of the study treatment for a particular
110 patient, and treatment availability at the study site. Eligible and consenting patients were
111 assigned in a ratio of 2:1 to either usual standard of care or usual standard of care plus
112 hydroxychloroquine or one of the other available treatment arms (see Supplementary Appendix)
113 using web-based simple (unstratified) randomization with allocation concealment. Patients
114 allocated to hydroxychloroquine sulfate (200mg tablet containing 155mg base equivalent)
115 received a loading dose of 4 tablets (800 mg) at zero and 6 hours, followed by 2 tablets (400
116 mg) starting at 12 hours after the initial dose and then every 12 hours for the next 9 days or until
117 discharge (whichever occurred earlier) (see Supplementary Appendix).¹⁵ Allocated treatment
118 was prescribed by the attending clinician. Participants and local study staff were not blinded to
119 the allocated treatment.

120 **Procedures**

121 A single online follow-up form was to be completed when participants were discharged, had
122 died or at 28 days after randomization (whichever occurred earlier). Information was recorded
123 on adherence to allocated study treatment, receipt of other study treatments, duration of
124 admission, receipt of respiratory support (with duration and type), receipt of renal dialysis or
125 hemofiltration, and vital status (including cause of death). From 12 May 2020, extra information

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126 was recorded on the occurrence of new major cardiac arrhythmia. In addition, routine health
127 care and registry data were obtained including information on vital status (with date and cause
128 of death); discharge from hospital; respiratory and renal support therapy.

129 **Outcome measures**

130 Outcomes were assessed at 28 days after randomization, with further analyses specified at 6
131 months. The primary outcome was all-cause mortality. Secondary outcomes were time to
132 discharge from hospital and, among patients not on invasive mechanical ventilation at
133 randomization, invasive mechanical ventilation (including extra-corporal membrane
134 oxygenation) or death. Subsidiary clinical outcomes included cause-specific mortality, use of
135 hemodialysis or hemofiltration, major cardiac arrhythmia (recorded in a subset), and receipt and
136 duration of ventilation.

137 **Statistical Analysis**

138 For the primary outcome of 28-day mortality, the log-rank 'observed minus expected' statistic
139 and its variance were used to both test the null hypothesis of equal survival curves and to
140 calculate the one-step estimate of the average mortality rate ratio, comparing all patients
141 allocated hydroxychloroquine with all patients allocated usual care. The few patients (2.1%) who
142 had not been followed for 28 days by the time of the data cut (22 June 2020) were either
143 censored on 22 June 2020 or, if they had already been discharged alive, were right-censored
144 for mortality at day 29 (that is, in the absence of any information to the contrary they were
145 assumed to have survived 28 days). Kaplan-Meier survival curves were constructed to display
146 cumulative mortality over the 28-day period. The same methods were used to analyze time to
147 hospital discharge, with patients who died in hospital right-censored on day 29. Median time to
148 discharge was derived from the Kaplan-Meier estimates. For the pre-specified composite
149 secondary outcome of invasive mechanical ventilation or death within 28 days (among those not

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150 receiving invasive mechanical ventilation at randomization), the precise date of starting invasive
151 mechanical ventilation was not available and so the risk ratio was estimated instead. Estimates
152 of absolute risk differences between patients allocated hydroxychloroquine and patients
153 allocated usual care were also calculated.

154 Pre-specified analyses of the primary outcome were performed in five subgroups defined by
155 characteristics at randomization: age, sex, level of respiratory support, days since symptom
156 onset, and predicted 28-day mortality risk (See Supplementary Appendix). One further pre-
157 specified subgroup analysis (ethnicity) will be conducted once data collection is completed.
158 Observed effects within subgroup categories were compared using a chi-square test for trend
159 (which is equivalent to a test for heterogeneity for subgroups that have only two levels).

160 Estimates of rate and risk ratios (both hereon denoted RR) are shown with 95% confidence
161 intervals. All p-values are 2-sided and are shown without adjustment for multiple testing. All
162 analyses were done according to the intention-to-treat principle. The full database is held by the
163 study team which collected the data from study sites and performed the analyses at the Nuffield
164 Department of Population Health, University of Oxford.

165 **Sample size and decision to stop enrolment**

166 As stated in the protocol, appropriate sample sizes could not be estimated when the trial was
167 being planned at the start of the COVID-19 pandemic. As the trial progressed, the Trial Steering
168 Committee, blinded to the results of the study treatment comparisons, formed the view that if
169 28-day mortality was 20% then a comparison of at least 2000 patients allocated to active drug
170 and 4000 to usual care alone would yield at least 90% power at two-sided $P=0.01$ to detect a
171 proportional reduction of one-fifth (a clinically relevant absolute difference of 4 percentage
172 points between the two arms).

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173 The independent Data Monitoring Committee reviewed unblinded analyses of the study data
174 and any other information considered relevant at intervals of around 2 weeks. The committee
175 was charged with determining if, in their view, the randomized comparisons in the study
176 provided evidence on mortality that is strong enough (with a range of uncertainty around the
177 results that is narrow enough) to affect national and global treatment strategies. In such a
178 circumstance, the Committee would inform the Trial Steering Committee who would make the
179 results available to the public and amend the trial arms accordingly. Unless that happened, the
180 Trial Steering Committee, investigators, and all others involved in the trial would remain blind to
181 the interim results until 28 days after the last patient had been randomized to a particular
182 intervention arm.

183 On 4 June, in response to a request from the MHRA, the independent Data Monitoring
184 Committee conducted a review of the data and recommended the chief investigators review the
185 unblinded data on the hydroxychloroquine arm of the trial. The Chief Investigators and Trial
186 Steering Committee concluded that the data showed no beneficial effect of hydroxychloroquine
187 in patients hospitalized with COVID-19. Therefore enrolment of participants to the
188 hydroxychloroquine arm was closed on 5 June and the preliminary result for the primary
189 outcome was made public. Investigators were advised that any patients currently taking
190 hydroxychloroquine as part of the study should discontinue the treatment.

191

192 **RESULTS**

193 **Patients**

194 Of the 11,197 patients randomized while the hydroxychloroquine arm was open (25 March to 5
195 June 2020), 7513 (67%) were eligible to be randomized to hydroxychloroquine (that is
196 hydroxychloroquine was available in the hospital at the time and the attending clinician was of

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197 the opinion that the patient had no known indication for or contraindication to
198 hydroxychloroquine) (Figure 1 and Table S1). Of these, 1561 were randomized to
199 hydroxychloroquine and 3155 were randomized to usual care with the remainder being
200 randomized to one of the other treatment arms. Mean age of study participants in this
201 comparison was 65.3 (SD 15.3) years (Table 1) and 38% patients were female. No children
202 were enrolled in the hydroxychloroquine comparison. A history of diabetes was present in 27%
203 of patients, heart disease in 26%, and chronic lung disease in 22%, with 57% having at least
204 one major comorbidity recorded. In this analysis, 90% of patients had laboratory confirmed
205 SARS-CoV-2 infection, with the result currently awaited for 1%. At randomization, 17% were
206 receiving invasive mechanical ventilation or extracorporeal membrane oxygenation, 60% were
207 receiving oxygen only (with or without non-invasive ventilation), and 24% were receiving neither.
208 Follow-up information was complete for 4619 (98%) of the randomized patients. Among those
209 with a completed follow-up form, 1395 (92%) patients allocated to hydroxychloroquine received
210 at least 1 dose (Table S2) and the median number of days of treatment was 6 days (IQR 3 to 10
211 days). 13 (0.4%) of the usual care arm received hydroxychloroquine. Use of azithromycin or
212 other macrolide drug during the follow-up period was similar in both arms (17% vs. 19%) as was
213 use of dexamethasone (8% vs. 9%).

214 **Primary outcome**

215 There was no significant difference in the proportion of patients who met the primary outcome of
216 28-day mortality between the two randomized arms (418 [26.8%] patients in the
217 hydroxychloroquine arm vs. 788 [25.0%] patients in the usual care arm; rate ratio, 1.09; 95%
218 confidence interval [CI], 0.96 to 1.23; P=0.18) (Figure 2). Similar results were seen across all
219 five pre-specified subgroups (Figure 3). In post hoc exploratory analyses restricted to the 4234
220 (90%) patients with a positive SARS-CoV-2 test result, the result was similar (rate ratio, 1.09, 95%
221 CI 0.96 to 1.24).

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222 **Secondary outcomes**

223 Allocation to hydroxychloroquine was associated with a longer time until discharge alive from
224 hospital than usual care (median 16 days vs. 13 days) and a lower probability of discharge alive
225 within 28 days (rate ratio 0.92, 95% CI 0.85 to 0.99) (Table 2). Among those not on invasive
226 mechanical ventilation at baseline, the number of patients progressing to the pre-specified
227 composite secondary outcome of invasive mechanical ventilation or death was higher among
228 those allocated to hydroxychloroquine (risk ratio 1.12, 95% CI 1.01 to 1.25).

229 **Subsidiary outcomes**

230 Information on the occurrence of new major cardiac arrhythmia was collected for 698 (44.7%)
231 patients in the hydroxychloroquine arm and 1357 (43.0%) in the usual care arm since these
232 fields were added to the follow-up form on 12 May 2020. Among these patients, there were no
233 significant differences in the frequency of supraventricular tachycardia (6.9% vs. 5.9%),
234 ventricular tachycardia or fibrillation (0.9% vs. 0.7%) or atrioventricular block requiring
235 intervention (0.1% vs. 0.1%) (Table S3). Analyses of cause-specific mortality, receipt of renal
236 dialysis or hemofiltration, and duration of ventilation will be presented once all relevant
237 information (including certified cause of death) is available. There was one report of a serious
238 adverse reaction believed related to hydroxychloroquine; a case of torsades de pointes from
239 which the patient recovered without the need for intervention.

240

241 **DISCUSSION**

242 Although preliminary, these results indicate that hydroxychloroquine is not an effective treatment
243 for patients hospitalized with COVID-19. The lower bound of the confidence limit for the primary
244 outcome rules out any reasonable possibility of a meaningful mortality benefit. In addition,
245 allocation to hydroxychloroquine was associated with an increase in the duration of

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246 hospitalization and an increased risk of requiring invasive mechanical ventilation or dying for
247 those not on invasive mechanical ventilation at baseline. The results were consistent across
248 subgroups of age, sex, time since illness onset, level of respiratory support, and baseline-
249 predicted risk.

250 RECOVERY is a large, pragmatic, randomized, controlled platform trial designed to provide
251 rapid and robust assessment of the impact of readily available potential treatments for COVID-
252 19 on 28-day mortality. Around 15% of all patients hospitalized with COVID-19 in the UK over
253 the study period were enrolled in the trial and the fatality rate in the usual care arm is consistent
254 with the hospitalized case fatality rate in the UK and elsewhere.^{7,29,30} Only essential data were
255 collected at hospital sites with additional information (including long-term mortality) ascertained
256 through linkage with routine data sources. We did not collect information on physiological,
257 electrocardiographic, laboratory or virologic parameters.

258 Hydroxychloroquine has been proposed as a treatment for COVID-19 based largely on its *in*
259 *vitro* SARS-CoV-2 antiviral activity and on data from observational studies reporting effective
260 reduction in viral loads. However, the 4-aminoquinoline drugs are relatively weak antivirals.¹⁵
261 Demonstration of therapeutic efficacy of hydroxychloroquine in severe COVID-19 would require
262 rapid attainment of efficacious levels of free drug in the blood and respiratory epithelium.³¹ Thus,
263 to provide the greatest chance of providing benefit in life threatening COVID-19, the dose
264 regimen was designed to result in rapid attainment and maintenance of plasma concentrations
265 that were as high as safely possible.¹⁵ These concentrations were predicted to be at the upper
266 end of those observed during steady state treatment of rheumatoid arthritis with
267 hydroxychloroquine.³² Our dosing schedule was based on hydroxychloroquine pharmacokinetic
268 modelling referencing a SARS-CoV-2 half maximal effective concentration (EC₅₀) of 0.72 µM
269 scaled to whole blood concentrations and an assumption that cytosolic concentrations in the
270 respiratory epithelium are in dynamic equilibrium with blood concentrations.^{8,15,33}

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271 The primary concern with short-term high dose 4-aminoquinoline regimens is cardiovascular
272 toxicity. Hydroxychloroquine causes predictable prolongation of the electrocardiograph QT
273 interval that is exacerbated by co-administration with azithromycin, as widely prescribed in
274 COVID-19 treatment.¹⁶⁻¹⁸ Although torsade de pointes has been described, serious
275 cardiovascular toxicity has been reported very rarely despite the high prevalence of
276 cardiovascular disease in hospitalized patients, the common occurrence of myocarditis in
277 COVID-19, and the extensive use of hydroxychloroquine and azithromycin together. The
278 exception is a Brazilian study which was stopped early because of cardiotoxicity. However in
279 that study, chloroquine 600 mg base was given twice daily for ten days, a substantially higher
280 total dose than used in other trials, including RECOVERY.^{34,35} Pharmacokinetic modelling in
281 combination with blood concentration and mortality data from a case series of 302 chloroquine
282 overdose patients predicts that the base equivalent chloroquine regimen to the RECOVERY
283 hydroxychloroquine regimen is safe.³⁵ Hydroxychloroquine is considered to be safer than
284 chloroquine.¹⁵ We did not observe excess mortality in the first 2 days of treatment with
285 hydroxychloroquine, the time when early effects of dose-dependent toxicity might be expected.
286 Furthermore, the preliminary data presented here did not show any excess in ventricular
287 tachycardia (including torsade de pointes) or ventricular fibrillation in the hydroxychloroquine
288 arm.

289 The findings indicate that hydroxychloroquine is not an effective treatment for hospitalized
290 patients with COVID-19 but do not address its use as prophylaxis or in patients with less severe
291 SARS-CoV-2 infection managed in the community. Treatment of COVID-19 with chloroquine or
292 hydroxychloroquine has been recommended in many treatment guidelines, including in Brazil,
293 China, France, Italy, Netherlands, South Korea, and the United States.³⁶ In a retrospective
294 cohort study in the United States, 59% of 1376 COVID-19 patients received
295 hydroxychloroquine.^{22,37} Since our preliminary results were first made public on 5 June 2020,

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296 the U.S. Food and Drugs Administration has revoked the Emergency Use Authorization that
297 allowed hydroxychloroquine and chloroquine to be used for hospitalized patients with COVID-
298 19,³⁸ and the World Health Organization (WHO) and the National Institutes for Health have
299 ceased trials of its use in this setting on the grounds of lack of benefit. The WHO has recently
300 released preliminary results from the SOLIDARITY trial on the effectiveness of
301 hydroxychloroquine in hospitalized COVID-19 patients that are consistent with the results from
302 the RECOVERY trial.³⁹

303

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304 **Authorship**

305 This manuscript was initially drafted by the first and last author, developed by the Writing
306 Committee, and approved by all members of the Trial Steering Committee. The funders had no
307 role in the analysis of the data, preparation and approval of this manuscript, or the decision to
308 submit it for publication. The first and last members of the Writing Committee vouch for the data
309 and analyses, and for the fidelity of this report to the study protocol and data analysis plan.

310

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362 Janet Wittes.

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391 **Conflicts of interest**

392 The authors have no conflict of interest or financial relationships relevant to the submitted work
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395 The Nuffield Department of Population Health at the University of Oxford has a staff policy of not
396 accepting honoraria or consultancy fees directly or indirectly from industry (see
397 <https://www.ndph.ox.ac.uk/files/about/ndph-independence-of-research-policy-jun-20.pdf>).

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489 **Table and figures**

490

491 **Table 1: Baseline characteristics by randomized allocation**

492 Results are count (%), mean \pm standard deviation, or median (inter-quartile range).* No children
493 (aged <18 years) were enrolled. †Includes 6 pregnant women. †† SARS-Cov-2 test results are
494 captured on the follow-up form, so are currently unknown for some. All tests for difference in
495 baseline characteristics between treatment arms give $p>0.05$. The 'oxygen only' group includes
496 non-invasive ventilation. Severe liver disease defined as requiring ongoing specialist care.
497 Severe kidney impairment defined as estimated glomerular filtration rate <30 mL/min/1.73m². 9
498 (0.6%) patients allocated to hydroxychloroquine and 9 (0.3%) patients allocated to usual care
499 alone had missing data for days since symptom onset.

500

501 **Table 2: Effect of allocation to hydroxychloroquine on main study outcomes**

502 RR=rate ratio for the outcomes of 28-day mortality and hospital discharge, and risk ratio for the
503 outcome of receipt of invasive mechanical ventilation or death. CI=confidence interval.

504 * Analyses exclude those on invasive mechanical ventilation at randomization. For the pre-
505 specified composite secondary endpoint of receipt of invasive mechanical ventilation or death
506 the absolute risk difference was 3.3 percentage points (95% CI 0.3 to 6.3).

507

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

509 ITT=intention to treat. * Number recruited overall during period that adult participants could be
510 recruited into hydroxychloroquine comparison. # 1516/1561 (97.1%) and 3078/3155 (97.6%)
511 patients have a completed follow-up form at time of analysis. † includes 37/1561 (2.4%) patients
512 in the hydroxychloroquine arm and 89/3155 (2.8%) patients in the usual care arm allocated to
513 tocilizumab in accordance with protocol version 4.0 or later. 6 patients were additionally

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514 randomized to convalescent plasma vs control (1 [0.1%] patient allocated to hydroxychloroquine
515 arm vs 5 [0.2%] patients allocated to usual care) in accordance with protocol version 6.0.
516 Among the 167 sites that randomized at least 1 patient to the hydroxychloroquine comparison,
517 the median number randomized was 20 patients (inter-quartile range 11 to 41).

518

519 **Figure 2: 28-day mortality**

520 RR=rate ratio. CI=confidence interval. The RR is derived from the log-rank observed minus
521 expected statistic ($O - E$) and its variance (V) as the one-step estimate, through the formula
522 $\exp\left(\frac{O - E}{V}\right)$, and its 95% CI is given by $\exp\left(\frac{O - E}{V} \pm 1.96 \div \sqrt{V}\right)$. The number of
523 patients randomized and the number remaining at risk of death at the end of days 7, 14, 21 and
524 28 are shown beneath the plot.

525

526 **Figure 3: Effect of allocation to hydroxychloroquine on 28-day mortality by pre-specified** 527 **characteristics at randomization**

528 RR=rate ratio. CI=confidence interval. Subgroup-specific RR estimates are represented by
529 squares (with areas of the squares proportional to the amount of statistical information) and the
530 lines through them correspond to the 95% confidence intervals. The 'oxygen only' group
531 includes patients receiving non-invasive ventilation. The method used for calculating baseline-
532 predicted risk is described in the Supplementary Appendix. One further pre-specified subgroup
533 analysis (ethnicity) will be conducted once data collection is completed.

534

535

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536 **Table 1: Baseline characteristics by randomized allocation**

	Hydroxychloroquine (n = 1561)	Usual care (n = 3155)
Age, years	65.2 (15.2)	65.4 (15.4)
< 70*	925 (59%)	1874 (59%)
≥ 70 to < 80	342 (22%)	630 (20%)
≥ 80	294 (19%)	650 (21%)
Sex		
Male	961 (62%)	1974 (63%)
Female†	600 (38%)	1181 (37%)
Number of days since symptom onset	9 [5 to 14]	9 [5 to 13]
Number of days since hospitalisation	3 [1 to 6]	3 [1 to 5]
Respiratory support received		
No oxygen received	362 (23%)	750 (24%)
Oxygen only	938 (60%)	1873 (59%)
Invasive mechanical ventilation	261 (17%)	532 (17%)
Comorbidities		
Diabetes	427 (27%)	856 (27%)
Heart disease	422 (27%)	789 (25%)
Lung disease	334 (21%)	712 (23%)
Tuberculosis	4 (0%)	9 (0%)
HIV	8 (1%)	13 (0%)
Severe liver disease	18 (1%)	46 (1%)
Severe kidney impairment	111 (7%)	261 (8%)
Any of the above	882 (57%)	1807 (57%)
SARS-Cov-2 test result		
Positive	1393 (89%)	2841 (90%)
Negative	153 (10%)	291 (9%)
Test result not yet known††	15 (1%)	23 (1%)

537

538

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539 **Table 2: Effect of allocation to hydroxychloroquine on main study outcomes**

	Hydroxychloroquine (n = 1561)	Usual care (n = 3155)	RR (95% CI)
Primary outcome:			
28-day all-cause mortality	418 (26.8%)	788 (25.0%)	1.09 (0.96 to 1.23)
Secondary outcomes:			
Discharged from hospital within 28 days	941 (60.3%)	1982 (62.8%)	0.92 (0.85 to 0.99)
Receipt of mechanical ventilation or death*	388/1300 (29.8%)	696/2623 (26.5%)	1.12 (1.01 to 1.25)
Death	308/1300 (23.7%)	572/2623 (21.8%)	1.09 (0.96 to 1.23)
Invasive mechanical ventilation	118/1300 (9.1%)	215/2623 (8.2%)	1.11 (0.89 to 1.37)

540

541

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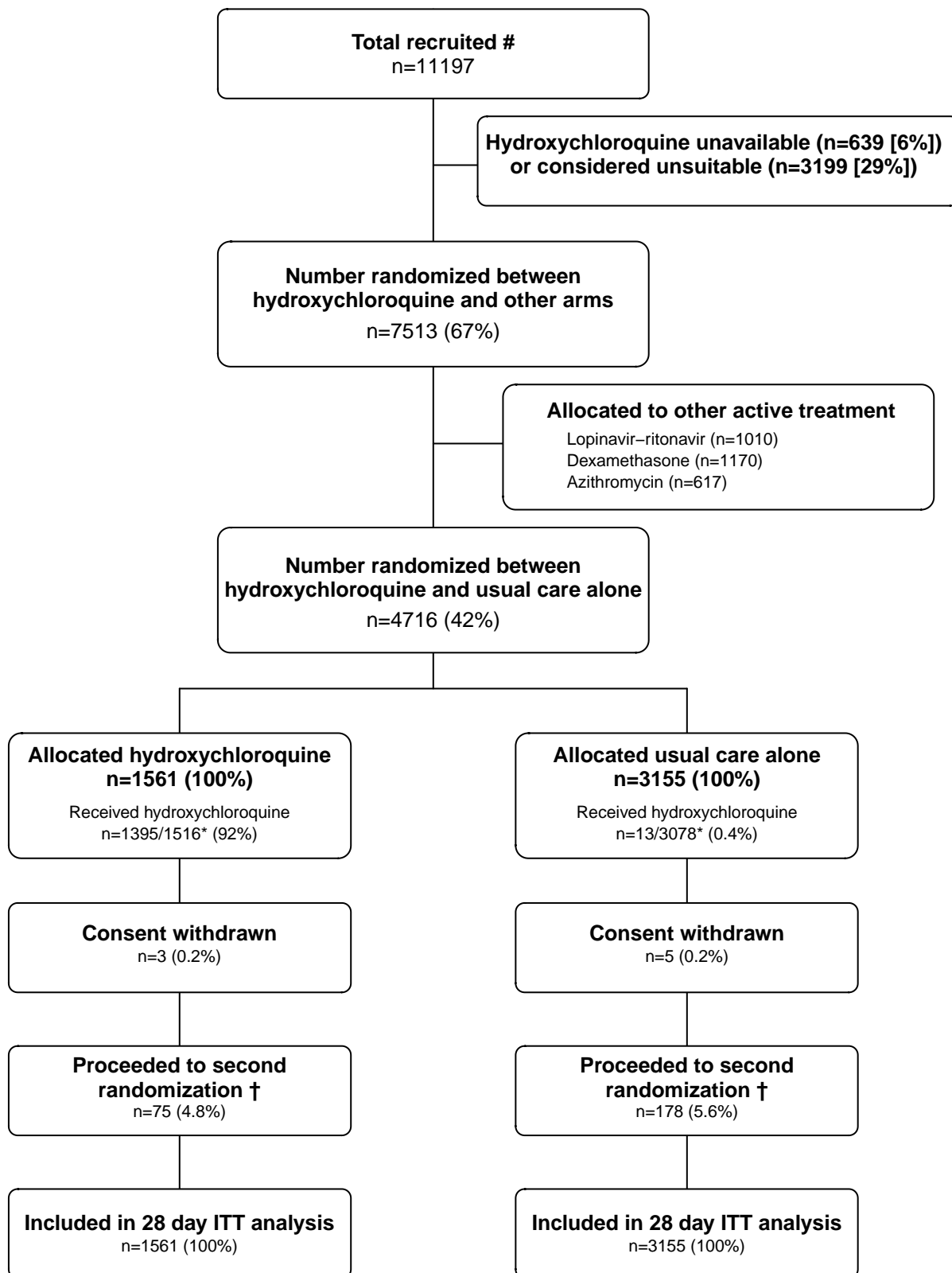
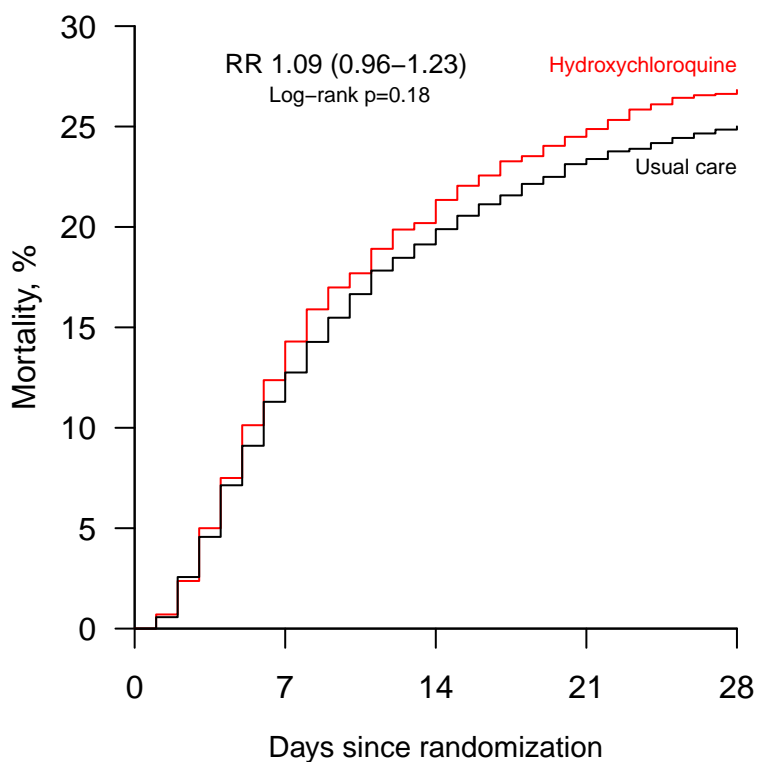


Figure 2: Effect of allocation to hydroxychloroquine on 28-day mortality

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Number at risk

Active

1561

1337

1227

1161

1125

Control

3155

2750

2525

2410

2346

Figure 3: Effects of allocation to hydroxychloroquine on 28-day mortality by baseline characteristics

