Al Presidente del Senato della Repubblica Italiana
On. Maria Elisabetta Alberti Casellati

Drusacco, 5 agosto 2020

<u>OGGETTO</u>: Petizione per la revoca del D.L. n. 83 del 30/07/2020 recante *"Misure urgenti connesse con la scadenza della dichiarazione di emergenza epidemiologica da COVID-19 deliberata il 31 gennaio 2020"* e per il ripristino dell'autorizzazione all'utilizzo di clorochina e analoghi nella terapia del COVID-19 al di fuori degli studi clinici.

La presente petizione per richiedere **un provvedimento per la revoca del D.L. n. 83 del 30/07/2020 (G.U. n. 190, 30/07/2020) in oggetto, comprendente la proroga al 15/10/2020 dello Stato di Emergenza deliberato il 31/01/2020** (Delibera del Consiglio dei Ministri - G.U. n. 26, 01/02/2020), in quanto al momento attuale non sussiste alcuna ragione per tale proroga – ammesso che fosse legittima la delibera iniziale del 31/01/2020 – e quindi non sussistono le premesse sulla base delle quali il decreto legge in oggetto è stato emanato. Inoltre, con la presente, si intende richiedere **un intervento presso l'AIFA (Agenzia Nazionale del Farmaco) per il ripristino dell'autorizzazione all'utilizzo di clorochina e analoghi nella terapia del COVID-19 al di fuori degli studi clinici, autorizzazione allo stato attuale sospesa**.

Secondo i dati ufficiali diramati dalla Protezione Civile, peraltro probabilmente di discutibile valore, il **numero totale di pazienti ricoverati in Italia risultati positivi al SARS-CoV-2** al 29 luglio, il giorno in cui il Senato ha approvato la proroga dello Stato di Emergenza, era di 769 unità, di cui 38 ricoverati in terapia intensiva, un **numero veramente esiguo** in confronto a quello della popolazione italiana, rappresentando poco più di una persona su centomila, quindi non certo tale da richiedere interventi di urgenza, tantopiù che il numero dei ricoverati è in progressivo calo, e questo nonostante la sospensione, da parte dell'AIFA, dell'autorizzazione all'utilizzo del farmaco dimostratosi maggiormente efficace per la terapia del COVID-19, la clorochina e i suoi analoghi, in particolare l'idrossiclorochina. Ciò sembrerebbe indicare, come d'altra parte sostenuto da molti esperti, che l'aggressività del virus si stia rapidamente affievolendo.

Neppure ha senso l'aver prorogato lo stato di emergenza in previsione di una possibile fantomatica seconda ondata in un prossimo futuro. Non bisogna ignorare il fatto che lo stato di emergenza di rilievo nazionale (artt. 7, 24 del Codice della Protezione Civile, D. Lgs. 1/18) prevede che ci sia un'emergenza in atto **di intensità ed estensione tali da richiedere mezzi e poteri eccezionali**, non una potenziale futura emergenza. Peraltro, non c'è alcuna base scientifica per la quale dovrebbe verificarsi una nuova ondata, a meno che non sia in programma una diffusione volontaria di virus, ma in questo caso l'unico intervento che ha senso intraprendere è l'immediata azione penale nei confronti di chi intende porre in essere un simile atto criminale, associata all'immediata chiusura dei laboratori di biosicurezza di livello 3 e 4. Volendo escludere questa possibilità, la giustificazione della proroga può solo avvenire mettendo

in atto una campagna mediatica di natura terroristica ed eventualmente causando morti effettive ricorrendo a protocolli “terapeutici” criminali.

In relazione a quanto sopra, desidero richiamare l’attenzione su due importantissimi aspetti.

1. **<u>Idrossiclorochina</u>**

   Non si può ignorare il fatto che la **clorochina e analoghi, in particolare l’idrossiclorochina**, farmaci utilizzati come antimalarici da più di cent’anni e impiegati anche nella terapia di alcune malattie autoimmuni, economici e con poche controindicazioni e scarsissimi effetti collaterali, **sono estremamente efficaci per la profilassi del COVID-19 nonché per la terapia della malattia**, soprattutto se essa viene avviata negli stadi iniziali. L’idrossiclorochina si è dimostrata particolarmente efficace in combinazione con l’azitromicina, e questa terapia combinata azzera la carica virale nel giro di una settimana al massimo, in tal modo riducendo anche la probabilità di contagio. Anche in Italia (come riportato da diverse testate verso fine aprile), si è osservata una netta riduzione dei casi gravi e ospedalizzati, in seguito all’estensione a livello territoriale dell’utilizzo dell’idrossi-clorochina.

   Eppure **l’AIFA**, in seguito ad una decisione dell’OMS (Organizzazione Mondiale della Sanità) basata su uno studio retrospettivo (M.R. Mehra, S.S. Desai, F. Ruschitzka, A.N. Patel “*Hydroxychloroquine or chloroquine with or without a matrolide for treatment of COVID-19: a multinational registry analysis*”) pubblicato il 22 maggio 2020 dalla rivista *The Lancet* – studio assolutamente inqualificabile, al punto da dover essere ritirato dalla rivista stessa –, **ne ha impedito l’utilizzo**, e allo stato attuale questo farmaco non è ancora autorizzato se non in studi clinici. Nella scheda relativa all’idrossiclorochina, l’AIFA scrive “*considerate le premesse sopra descritte, l’uso dell’idrossiclorochina, da sola o in associazione ad altri farmaci, non è autorizzato al di fuori degli studi clinici.*”

   Conseguentemente al ritiro da parte del *The Lancet* dell’articolo di cui sopra, l’OMS ha revocato la decisione di sospendere l’utilizzo dell’idrossiclorochina, ma l’ha successivamente riconfermata in seguito alle risultanze di uno studio clinico, il *Recovery trial*, condotto dall’Università di Oxford; tali risultanze avevano sollevato preoccupazioni riguardo alla sicurezza e alla mancanza di efficacia. Questa notizia, a cui era stato dato notevole risalto mediatico e la quale era stata ripresa persino dallo Spallanzani, aveva l’unico fine di creare diffidenza nei confronti dell’unico farmaco sinora rivelatosi di sicura efficacia nella terapia e nella profilassi del COVID-19. Sono state invece completamente ignorate dall’OMS e dall’AIFA e puntualmente taciute dai media *mainstream* le risultanze di ulteriori studi successivi, tra cui lo studio randomizzato “*Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19*”, pubblicato nella rivista *International Journal of Infectious Diseases* il 1 luglio 2020 e condotto dall’Ospedale Henry Ford di Detroit su 3000 pazienti, in base al quale si è osservata una significativa riduzione della percentuale

di decessi nei gruppi trattati con idrossiclorochina da sola o in combinazione con azitromicina rispetto al gruppo di controllo.
D'altra parte, **la clorochina e i suoi analoghi hanno dimostrato la loro efficacia per la terapia dell'influenza spagnola, della SARS, dell'aviaria, della MERS, e probabilmente si dimostrerebbero efficaci per molte altre sindromi influenzali**, anche stando a quanto emerge dagli studi e dalle dichiarazioni del ricercatore dell'ISS (Istituto Superiore della Sanità) Andrea Savarino (A. Savarino *et al*., "*Effects of chloroquine on viral infections: an old drug against today's diseases*?", *The Lancet*, 2003; intervista ad Andrea Savarino su Il Tempo del 21-04-2020 "*Idrossiclorochina, così il farmaco anti-malaria previene il Coronavirus*").
Alla luce di queste conoscenze, **continuare ad impedire l'utilizzo di clorochina e analoghi** (la cui efficacia per il trattamento del COVID-19 – si sottolinea – era già stata osservata nello studio cinese a firma Jianjun Gao, *et al*., "*Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies*", pubblicato il 19 febbraio 2020 e dimostrata dai vari studi successivi condotti dall'*équipe* del Prof. Didier Raoult dell'Ospedale Universitario di Marsiglia) **e insistere a sperimentare su umani nuovi farmaci già rivelatisi di dubbia o nulla efficacia** (Remdesivir, Lopinavir, Ritonavir, ecc.) e che per di più possono causare nel paziente seri effetti avversi (insufficienza epatica e renale) talora mortali, **significa CONTINUARE A PERPETRARE UN CRIMINE GRAVISSIMO**.

Non mi soffermo sul primo dei due studi citati sopra che hanno determinato la sospensione dell'uso di clorochina e analoghi da parte dell'OMS, ossia sullo studio poi ritirato. Sia sufficiente dire che questo studio era stato condotto sulla base dei dati forniti da un'azienda – la Surgisphere di Sapan Desai, coautore dell'articolo –, nel cui organico di sette persone figurano una *hostess* e modella in riviste "per adulti" e un autore di romanzi di fantascienza, e che tali dati, che si pretendeva provenissero da diversi ospedali nel mondo, sono stati dimostrati non corrispondere neppure a cifre reali (il numero di morti in Australia considerati nello studio superava il numero totale di morti attribuiti al COVID-19 in quel Paese).

Senza scendere troppo nel dettaglio, vorrei invece spendere qualche parola in più, per chi non ne fosse a conoscenza, sullo studio clinico *Recovery*, finanziato, *inter alia*, dal Wellcome Trust (All. 2, p. 18) e dalla fondazione di Bill Gates, lo stesso "filantropo" a cui sono stati promessi dal Presidente del Consiglio Giuseppe Conte 287,5 milioni di Euro dell'erario statale per lo sviluppo di un vaccino, quando è ormai chiaro a molti che, anche se questo fosse realmente efficace, non serve più a nulla perché ormai l'epidemia ha fatto il suo corso e ragionevolmente gran parte della popolazione è già naturalmente immunizzata.
Lo studio *Recovery* è stato condotto in ospedali inglesi dall'Università di Oxford, la quale anch'essa riceve costanti finanziamenti dalla Bill and Melinda Gates Foundation. Il protocollo di questo studio mette a confronto diverse terapie, somministrate a gruppi di pazienti che acconsentono, tramite firma, al reclutamento.

La firma è richiesta direttamente al paziente, se di età maggiore o uguale a **16 anni**, e solo in caso di pazienti al di sotto dei 16 anni ai genitori o a chi ne fa le veci (All. 2, p. 7). **Non è riportata alcuna approvazione da parte di alcun Comitato Bioetico** né interno agli ospedali che conducono lo studio, né tantomeno nazionale o internazionale.
Il protocollo prevede diversi bracci (All. 2, p. 21 e segg.) corrispondenti alle diverse terapie, tra cui appunto la terapia a base di idrossiclorochina e quella a base di azitromicina; tuttavia, non considera la possibilità di combinazione di diversi farmaci; la combinazione idrossiclorochina e azitromicina, notoriamente efficace, non è perciò prevista.
Il trattamento a base di idrossiclorochina viene somministrato a pazienti ospedalizzati, quindi, presumibilmente, già in gravi condizioni, quando è ormai risaputo che l'efficacia di questo farmaco è massima nelle prime fasi dell'infezione perché blocca l'evoluzione verso la fase infiammatoria.
Ma l'aspetto **più grave – criminale** – è che per il gruppo trattato con idrossiclorochina il protocollo *Recovery* prevede per gli adulti, nelle prime 12 ore, un dosaggio d'attacco di 1600 mg indipendentemente dal peso del paziente, dosaggio addirittura quadruplo rispetto al dosaggio di attacco massimo di 400 mg su 12 ore indicato sul foglietto illustrativo del Plaquenil (All. 4) e rispetto al dosaggio di attacco di 400 mg su 12 ore contemplato per la terapia del COVID-19 dal protocollo SIMIT (Società Italiana Malattie Infettive e Tropicali) del 27/03/2020 ("*Gestione domiciliare della terapia precoce COVID-19*", All. 3), per arrivare a 2000 mg al termine del primo giorno; prevede poi, durante i nove giorni successivi al primo, un dosaggio di 800 mg die, doppio rispetto a quello utilizzato per la terapia del COVID-19 in base al protocollo SIMIT (All. 3). Un dosaggio di **2000 mg in un solo giorno può, a seconda del peso del paziente adulto, persino superare il sovradosaggio considerato letale** (la dose letale stimata è 30-50 mg/kg – All. 5) ed è comunque tale da richiedere immediato intervento di disintossicazione. Ma ancora più preoccupante è il **dosaggio d'attacco pediatrico**, differenziato in base al peso corporeo del paziente, con scaglioni di 5-10-20 kg (All. 2, p. 28); questo dosaggio **scende, all'interno di ciascuno scaglione, da un massimo di 50 a un minimo 25 mg/kg al termine del primo giorno, e in bambini con peso superiore a 21 kg raggiunge la dose di 1 g, per poi attestarsi, in caso di peso corporeo maggiore di 40 kg, sulla dose di 2 g prevista per gli adulti. Si tratta di dosaggi ad elevatissimo rischio di letalità per i pazienti pediatrici**, tantopiù che i bambini hanno, rispetto agli adulti, una sensibilità molto maggiore agli effetti tossici del farmaco (persino a tracce che possano essere presenti nel latte materno), come avverte chiaramente in più punti il foglietto illustrativo del Plaquenil compresse 200 mg (All. 4). Il dosaggio di 50 mg/kg è previsto addirittura per **bambini con peso corporeo di 5 kg**, ed è quasi **otto volte la dose giornaliera massima di 6,5 mg/kg che nei bambini non bisogna "*mai superare*" (All. 4)**: questa dose massima pediatrica giornaliera corrisponde, per un bambino di 31 kg, a una compressa da 200 mg. Il documento di cui all'All. 5 cita, a questo proposito, casi di decessi in bambini dopo l'assunzione di una o due compresse.
Verosimilmente, il sovradosaggio previsto dal protocollo *Recovery* – corrispondente, secondo quanto affermato dallo studio stesso (All. 2, p. 22), a una dose doppia rispetto a

quella utilizzata per il trattamento della malaria, e ciò con l'asserito obiettivo di "*raggiungere concentrazioni nel plasma tale da inibire il virus nel tempo più breve e nel modo più sicuro possibile*" – **ha condotto a gravi effetti collaterali o addirittura alla morte** una buona percentuale dei pazienti soggetti al trattamento, e ha comunque determinato la decisione da parte della Gran Bretagna, *in primis*, e dell'OMS, a ruota, di **sospendere l'utilizzo dell'idrossiclorochina**, con enorme eco mediatico, riguardo alla tossicità del farmaco, in Italia e in molti altri Paesi nel mondo.

2. <u>Decessi totali</u>

Faccio riferimento alle curve cumulative dei decessi giorno per giorno, comune per comune, in Italia dal primo gennaio a fine maggio reperibili sul sito ISTAT (https://www.istat.it/it/archivio/241428). Si tratta di grafici che rappresentano il **numero di morti per qualunque causa, come risultanti dagli uffici anagrafe**, quindi senza distinzione del fatto che, al decesso, fossero considerati o meno positivi al COVID-19. È possibile mettere a confronto i dati relativi al 2020 coi dati relativi ad ognuno dei 5 anni precedenti dal 2015 al 2019.

Si osservano particolarità che lasciano a dir poco perplessi, ma ciò che è in primo luogo degno di nota è che, **a partire dalla seconda metà di aprile, su tutto il territorio italiano il numero di decessi giornalieri si è stabilizzato su valori sovrapponibili, quando non inferiori, a quelli degli anni precedenti e a quelli precedenti al picco di mortalità**, quindi la realtà dei fatti contraddice alla base la campagna mediatica, che si sta protraendo tuttora, riguardante l'elevata letalità del virus.

<u>*Prima particolarità*</u> (All. 1A): **sulla gran parte del territorio italiano i grafici del 2020 sono del tutto sovrapponibili a quelli dei cinque anni precedenti, se non al di sotto** (v. Firenze, Roma, Napoli) con curve cumulative praticamente lineari, ossia con numero di morti giornaliero pressoché costante. **Fanno eccezione le regioni occidentali e centrali del nord Italia**, dove in molti capoluoghi si ha comunque l'andamento descritto sopra, fino alle prime due, tre settimane di marzo, con numero di decessi inferiore ad almeno uno dei cinque anni precedenti. Ma poi, a partire **dalla terza o quarta settimana di marzo**, si osserva un'**impennata** più o meno rapida della curva (v. Milano). **Dopo circa un mese il numero di morti giornalieri ritorna ai valori precedenti all'impennata, e corrispondenti a quelli degli anni precedenti**. Visto che è ormai notorio che il COVID-19 stava imperversando in tutto il nord Italia già probabilmente da fine novembre, se non prima, e che a febbraio era al suo apice, sorge spontaneo chiedersi come mai prima della terza settimana di marzo la situazione era esattamente sovrapponibile a quella degli anni precedenti, e dopo c'è stata questa impennata di morti. Ricordo che l'individuazione del cosiddetto "paziente 1" (le ricerche del "paziente 0" mi risulta siano state sospese) risale al 26 febbraio. Anche volendo credere alla leggenda dei superdiffusori e considerare il "paziente 1" come tale, ci si chiede come sia possibile questa puntualità dell'esplosione dei decessi nei capoluoghi più colpiti. E ci si chiede altresì se per caso non abbia influito il fatto che, mentre prima dell'individuazione del paziente 1 i medici agivano secondo le conoscenze a loro disposizione, con antibiotici

associati a cortisonici nei casi più ostinati, dopo l'inizio ufficiale della cosiddetta "pandemia" l'unico farmaco autorizzato alla prescrizione da parte dei medici di base fino a fine marzo (cioè fino a quando non è stato finalmente autorizzato l'utilizzo a livello territoriale dell'idrossiclorochina) era la tachipirina, con conseguente frequente ingravescenza della sintomatologia e necessità di ricorrere a "cure" ospedaliere, che presumibilmente prevedevano l'applicazione di protocolli di sperimentazione di nuovi farmaci o il ricorso a trattamenti non idonei, quando non semplicemente il cosiddetto "accompagnamento alla morte" con morfina.

Seconda particolarità (All. 1B): **in tutti i capoluoghi della Lombardia** le curve hanno uno stesso andamento, con **impennata** più o meno ripida come descritto nel precedente paragrafo. **Fa eccezione Sondrio**, con una curva che rimane persino al di sotto della curva relativa al 2019. Volendo attribuire il *surplus* di morti al COVID-19, ci si chiede come mai questo comune pare indenne, se si pensa oltretutto che la provincia di Sondrio confina con quella di Bergamo, la più colpita in Italia.

Terza particolarità (All. 1C): nelle regioni del nord-est e in tutte le regioni del **centro e sud Italia i grafici sono del tutto sovrapponibili a quelli degli anni precedenti**, senza anomalie di sorta, con un numero di decessi inferiore rispetto ad almeno uno degli anni compresi tra il 2015 e il 2019 e con numero di morti giornalieri pressoché costante. L'unico capoluogo che **si differenzia è Pesaro, che ha una curva del tutto simile come forma a quelle dei capoluoghi lombardi**. Anche qui occorrerebbe investigare rigorosamente su quale sia la causa di questa anomalia. Peraltro c'è da osservare che le regioni meridionali hanno registrato un numero di decessi inferiore rispetto ad almeno uno degli anni precedenti tra il 2015 e il 2019, e questo nonostante il massiccio rientro di meridionali proprio dalla Lombardia, ossia il focolaio di Italia, in seguito all'annuncio della definizione della "zona rossa".

In conclusione, **nulla ha giustificato la proroga dello Stato di Emergenza**, in quanto:

- anche dando credibilità ai dati ufficiali, **i ricoverati per COVID-19 sono in progressivo calo e allo stato attuale rappresentano, in rapporto alla popolazione italiana, poco più di una persona su centomila**, un'esigua minoranza rispetto ai portatori di altre infezioni batteriche o virali attive (tubercolosi, epatiti, ecc.);

- è comunque risaputo e dimostrato che **per il COVID-19 è nota una terapia efficace**, economica, e sicura, **a base di idrossiclorochina, in associazione con azitromicina** ed eventualmente eparina, la quale, se intrapresa tempestivamente, riduce drasticamente la probabilità di morte per effetto del virus;

- emerge chiaramente dai grafici che, ormai da fine aprile, il **numero di morti giornalieri per qualunque causa è esattamente sovrapponibile a quello degli anni passati**: questo evidenzia il fatto che **non c'è una situazione tale da giustificare una vita diversa da**

quella degli anni passati; peraltro, l'applicazione delle misure tuttora previste ai fini di protezione personale e distanziamento sociale segue criteri totalmente incoerenti, per non dire demenziali.

Al di là della paradossale giustificazione mediatica che vorrebbe che la proroga dello stato di emergenza fosse funzionale alla necessità di procurare, senza intralci di natura legislativa o burocratica, dispositivi di protezione personale e distanziamento, cosa di cui alla luce dei dati non si vede peraltro alcuna necessità, in realtà tale proroga pare del tutto pretestuosa, e con ogni probabilità le vere mire dietro a un ulteriore prolungamento della sospensione dei diritti costituzionali sono altre: affossare l'economia sana, incentivare la cosiddetta "Green" Economy, che di verde ha solo il nome, accentrare il potere nelle mani di grosse *lobby* economico-finanziarie, e tanti altri loschi obiettivi.

Pertanto, alla luce di tutte le considerazioni di cui sopra, SI RICHIEDE:

- **UN PROVVEDIMENTO DI REVOCA DEL D.L. n. 83 del 30/07/2020 RECANTE "Misure urgenti connesse con la scadenza della dichiarazione di emergenza epidemiologica da COVID-19 deliberata il 31 gennaio 2020."**
- **UN INTERVENTO PRESSO L'AIFA PER IL RIPRISTINO DELL'AUTORIZZAZIONE ALL'UTILIZZO DI CLOROCHINA E ANALOGHI NELLA TERAPIA DEL COVID-19 ANCHE AL DI FUORI DEGLI STUDI CLINICI**.

In fede.

Carla Young

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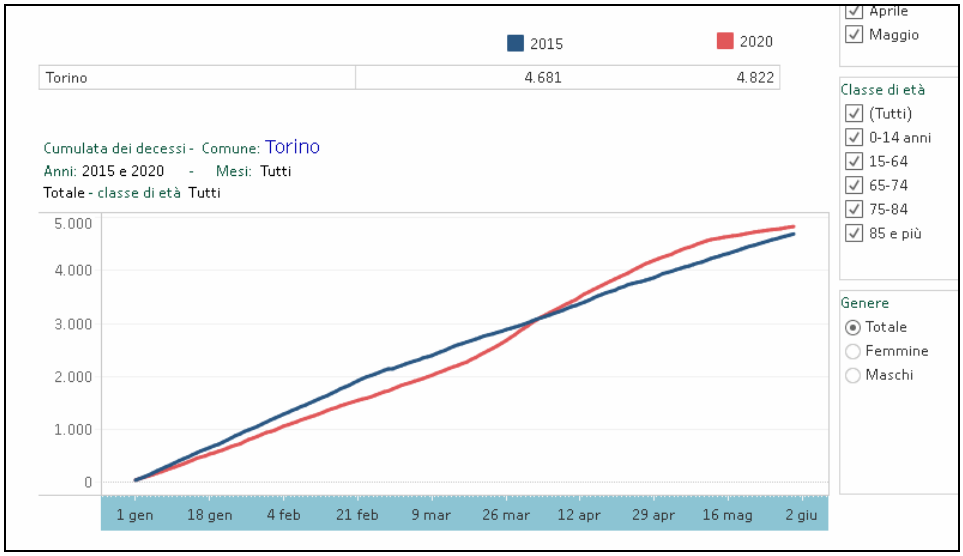
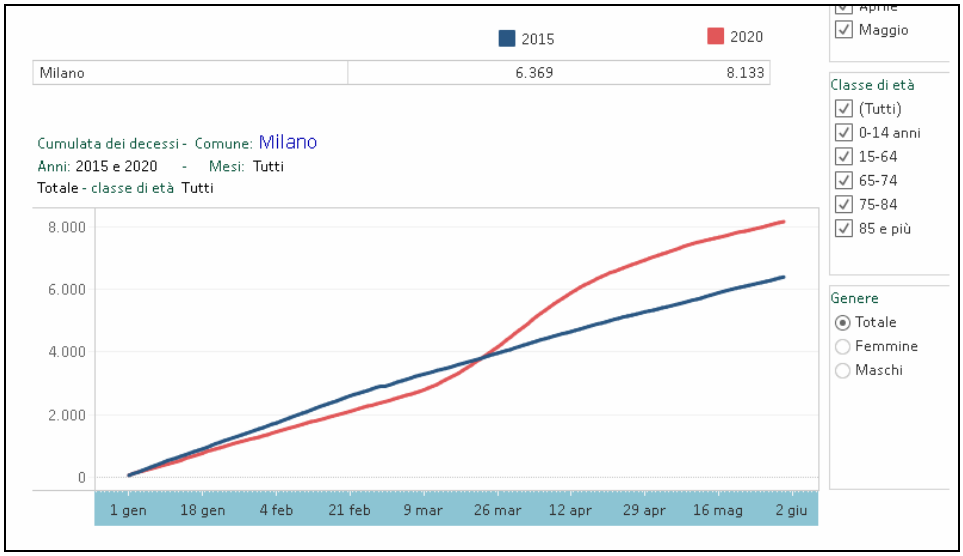
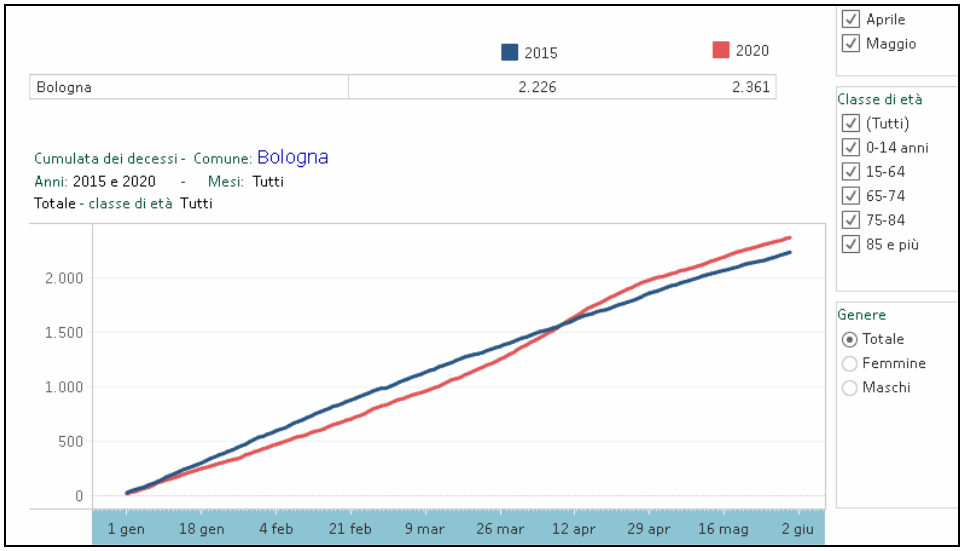
ALLEGATO 1 (fonte ISTAT)

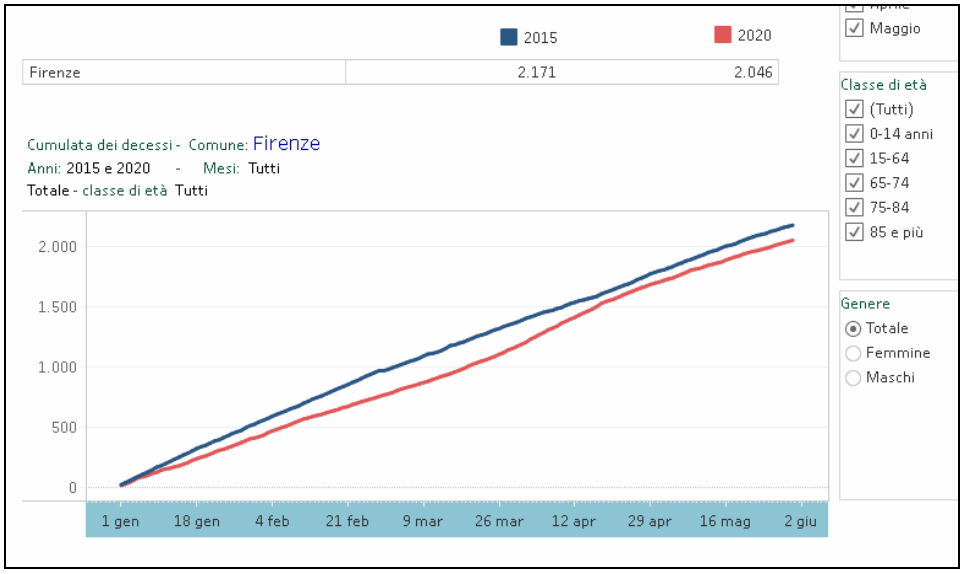
All. 1A

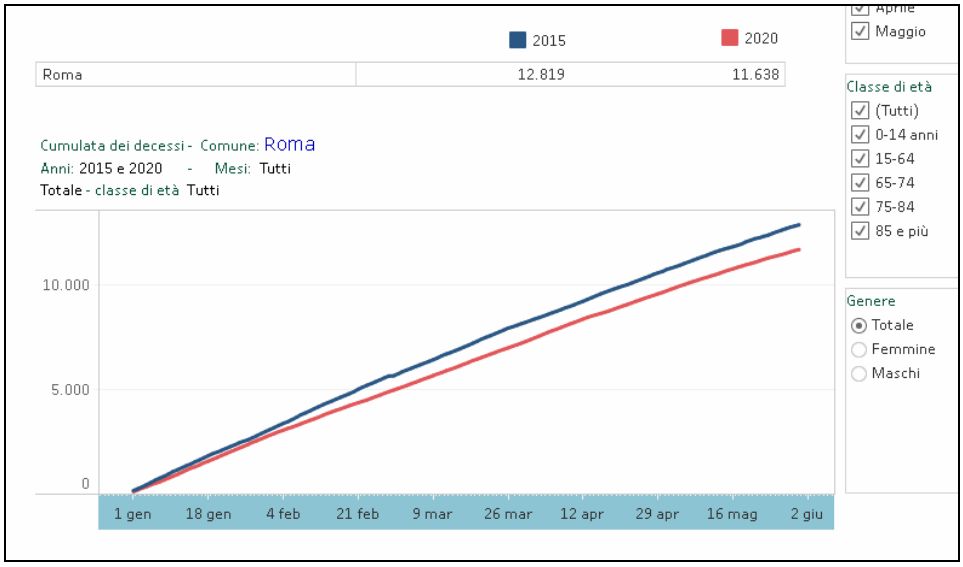
Andamento dei decessi per qualunque causa nelle maggiori città di Italia: Torino, Milano, Bologna, Firenze, Roma, Napoli.

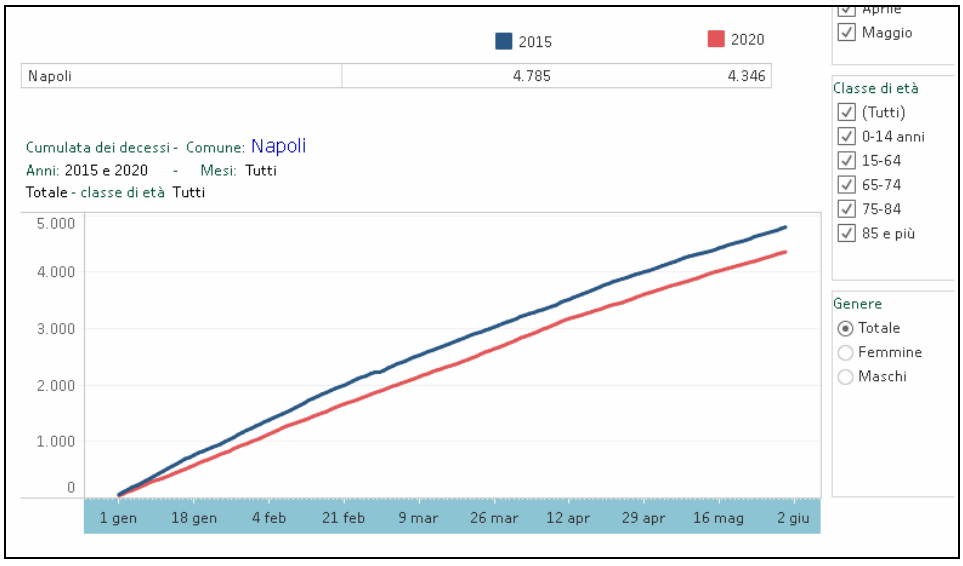






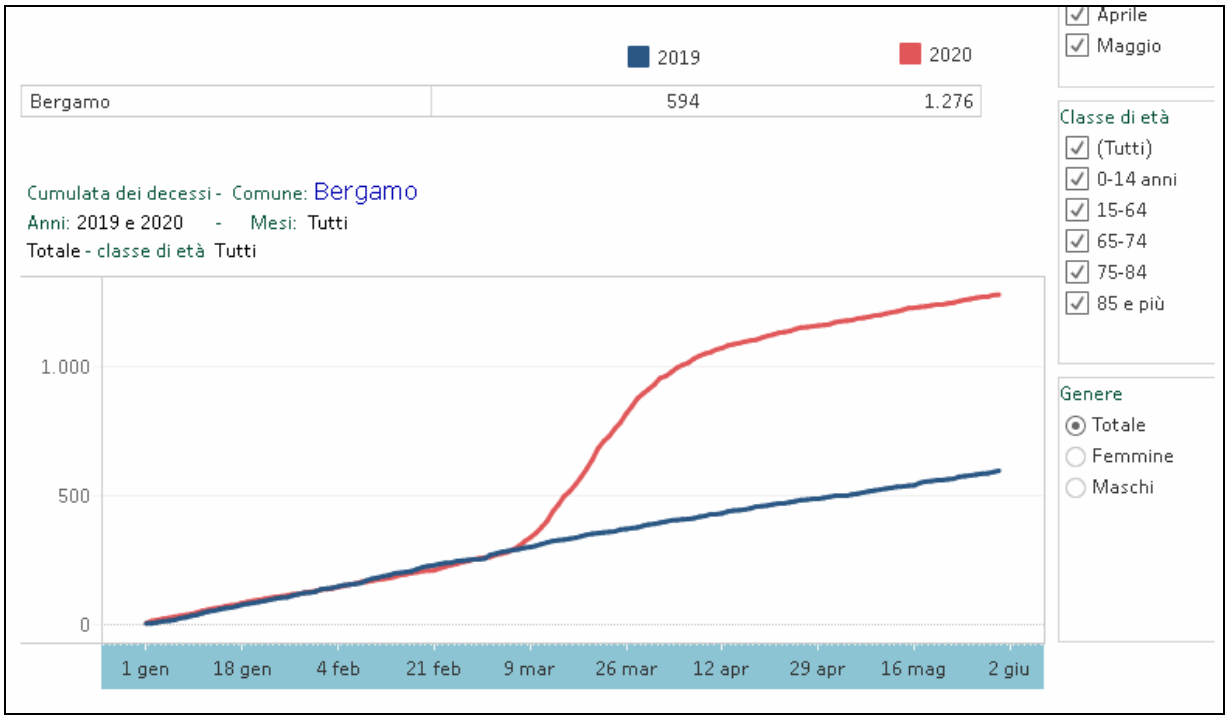

2015
2020
Firenze
2.171
2.046
Cumulata dei decessi - Comune: Firenze
Anni: 2015 e 2020 - Mesi: Tutti
Totale - classe di età Tutti
2.000
1.500
1.000
500
0
1 gen
18 gen
4 feb
21 feb
9 mar
26 mar
12 apr
29 apr
16 mag
2 giu
Maggio
Classe di età
(Tutti)
0-14 anni
15-64
65-74
75-84
85 e più
Genere
Totale
Femmine
Maschi

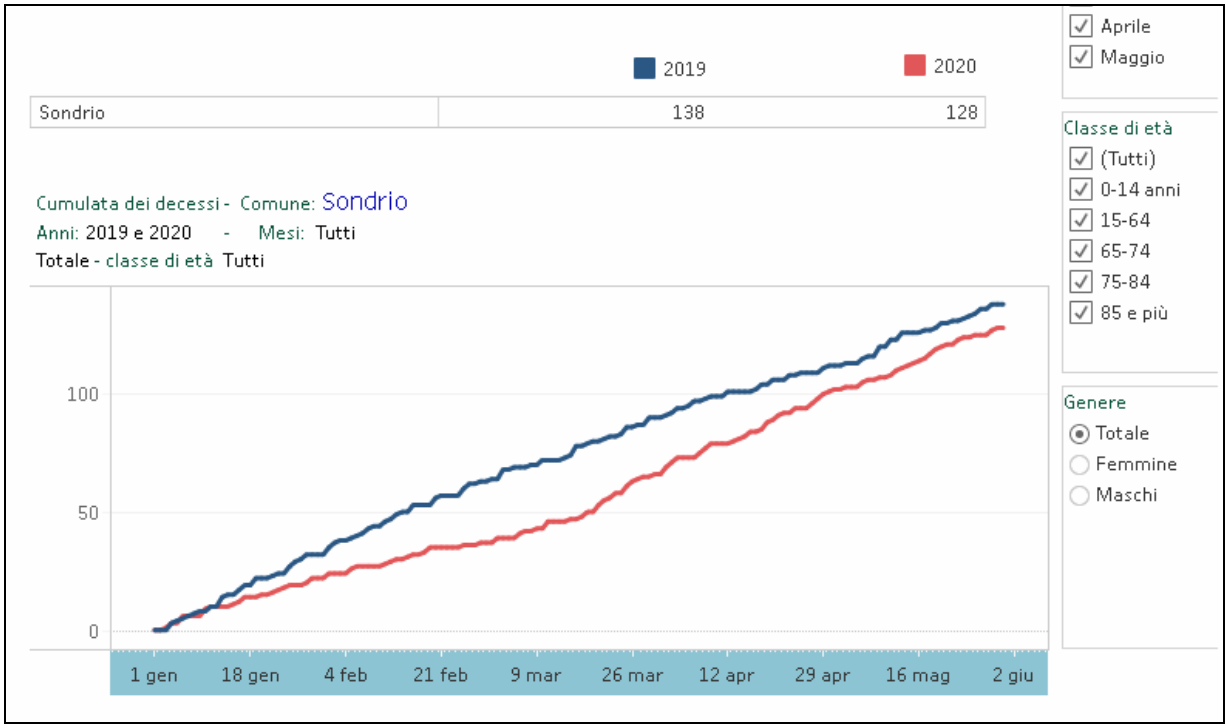

2015
2020
Roma
12.819
11.638
Cumulata dei decessi - Comune: Roma
Anni: 2015 e 2020 - Mesi: Tutti
Totale - classe di età Tutti
10.000
5.000
0
1 gen
18 gen
4 feb
21 feb
9 mar
26 mar
12 apr
29 apr
16 mag
2 giu
Maggio
Classe di età
(Tutti)
0-14 anni
15-64
65-74
75-84
85 e più
Genere
Totale
Femmine
Maschi


2015
2020
Napoli
4.785
4.346
Cumulata dei decessi - Comune: Napoli
Anni: 2015 e 2020 - Mesi: Tutti
Totale - classe di età Tutti
5.000
4.000
3.000
2.000
1.000
0
1 gen
18 gen
4 feb
21 feb
9 mar
26 mar
12 apr
29 apr
16 mag
2 giu
Maggio
Classe di età
(Tutti)
0-14 anni
15-64
65-74
75-84
85 e più
Genere
Totale
Femmine
Maschi

All. 1B

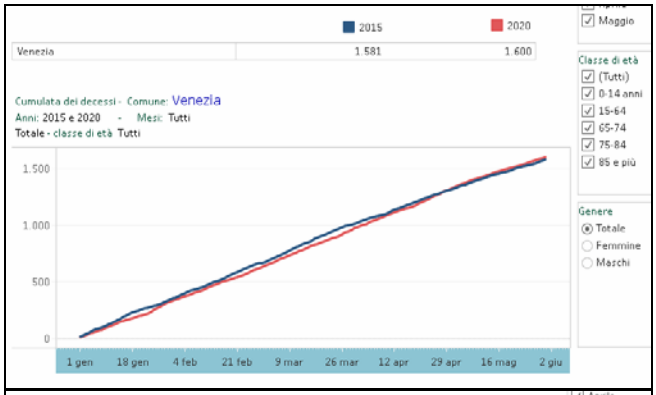
Andamento dei decessi per qualunque causa nei capoluoghi di due province confinanti: Sondrio e Bergamo.

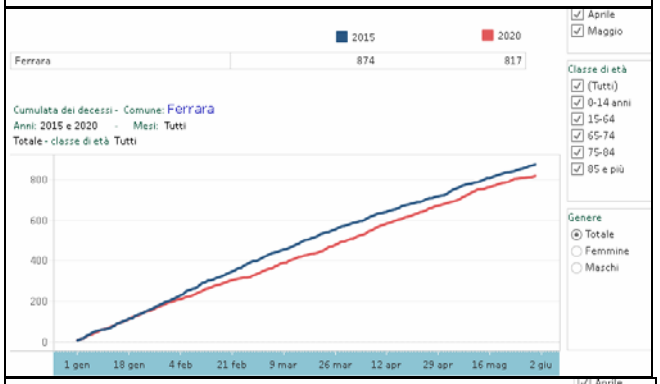


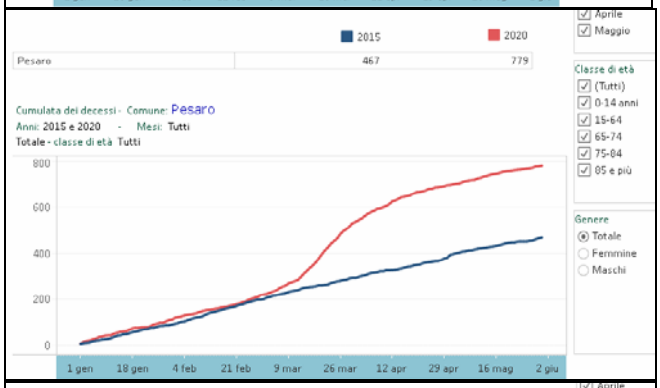


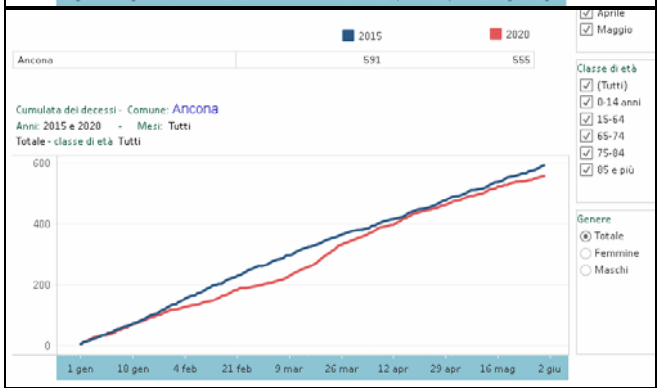
All. 1C

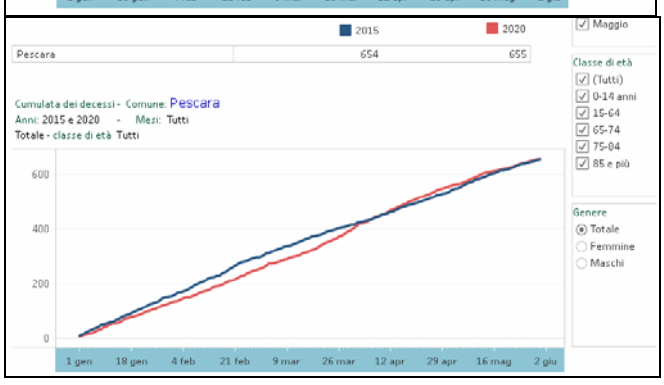
Andamento dei decessi per qualunque causa lungo il litorale adriatico: appare in tutta evidenza l'anomalia di Pesaro.











RANDOMISED EVALUATION OF COVID-19 THERAPY (RECOVERY)

Background: In early 2020, as this protocol was being developed, there were no approved treatments for COVID-19, a disease induced by the novel coronavirus SARS-CoV-2 that emerged in China in late 2019. The UK New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) advised that several possible treatments should be evaluated, including Lopinavir-Ritonavir, low-dose corticosteroids, and Hydroxychloroquine. These groups also advised that other treatments will soon emerge that require evaluation. A World Health Organization (WHO) expert group issued broadly similar advice.

Eligibility and randomisation: This protocol describes a randomised trial among patients hospitalised for COVID-19. All eligible patients are randomly allocated between several treatment arms, each to be given in addition to the usual standard of care in the participating hospital: No additional treatment *vs* lopinavir-ritonavir *vs* low-dose corticosteroids *vs* hydroxychloroquine *vs* azithromycin. In a factorial design, eligible patients are allocated simultaneously to no additional treatment *vs* convalescent plasma. The study allows a subsequent randomisation for patients with progressive COVID-19 (evidence of hyper-inflammatory state): No additional treatment *vs* tocilizumab. For patients for whom not all the trial arms are appropriate or at locations where not all are available, randomisation will be between fewer arms.

Adaptive design: The interim trial results will be monitored by an independent Data Monitoring Committee (DMC). The most important task for the DMC will be to assess whether the randomised comparisons in the study have provided evidence on mortality that is strong enough (with a range of uncertainty around the results that is narrow enough) to affect national and global treatment strategies. In such a circumstance, the DMC will inform the Trial Steering Committee who will make the results available to the public and amend the trial arms accordingly. New trial arms can be added as evidence emerges that other candidate therapeutics should be evaluated.

Outcomes: The main outcomes will be death, discharge, need for ventilation and need for renal replacement therapy. For the main analyses, follow-up will be censored at 28 days after randomisation. Additional information on longer term outcomes may be collected through review of medical records or linkage to medical databases such as those managed by NHS Digital and equivalent organisations in the devolved nations.

Simplicity of procedures: To facilitate collaboration, even in hospitals that suddenly become overloaded, patient enrolment (via the internet) and all other trial procedures are greatly streamlined. Informed consent is simple and data entry is minimal. Randomisation via the internet is simple and quick, at the end of which the allocated treatment is displayed on the screen and can be printed or downloaded. Follow-up information is recorded at a single timepoint and may be ascertained by contacting participants in person, by phone or electronically, or by review of medical records and databases.

Data to be recorded: At randomisation, information will be collected on the identity of the randomising clinician and of the patient, age, sex, major co-morbidity, pregnancy, COVID-19 onset date and severity, and any contraindications to the study treatments. The main

outcomes will be death (with date and probable cause), discharge (with date), need for ventilation (with number of days recorded) and need for renal replacement therapy. Reminders will be sent if outcome data have not been recorded by 28 days after randomisation. Suspected Unexpected Serious Adverse Reactions (SUSARs) to one of the study medications (e.g., Stevens-Johnson syndrome, anaphylaxis, aplastic anaemia) will be collected and reported in an expedited fashion. Other adverse events will not be recorded but may be available through linkage to medical databases.

Numbers to be randomised: The larger the number randomised the more accurate the results will be, but the numbers that can be randomised will depend critically on how large the epidemic becomes. If substantial numbers are hospitalised in the participating centres then it may be possible to randomise several thousand with mild disease and a few thousand with severe disease, but realistic, appropriate sample sizes could not be estimated at the start of the trial.

Heterogeneity between populations: If sufficient numbers are studied, it may be possible to generate reliable evidence in certain patient groups (e.g. those with major co-morbidity or who are older). To this end, data from this study may be combined with data from other trials of treatments for COVID-19, such as those being planned by the WHO.

Add-on studies: Particular countries or groups of hospitals, may well want to collaborate in adding further measurements or observations, such as serial virology, serial blood gases or chemistry, serial lung imaging, or serial documentation of other aspects of disease status. While well-organised additional research studies of the natural history of the disease or of the effects of the trial treatments could well be valuable (although the lack of placebo control may bias the assessment of subjective side-effects, such as gastro-intestinal problems), they are not core requirements.

To enquire about the trial, contact the RECOVERY Central Coordinating Office

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To RANDOMISE a patient, visit:

Website: www.recoverytrial.net

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1 BACKGROUND AND RATIONALE

1.1 Setting

In 2019 a novel coronavirus-induced disease (COVID-19) emerged in Wuhan, China. A month later the Chinese Center for Disease Control and Prevention identified a new beta-coronavirus (SARS coronavirus 2, or SARS-CoV-2) as the aetiological agent.[1] The clinical manifestations of COVID-19 range from asymptomatic infection or mild, transient symptoms to severe viral pneumonia with respiratory failure. As many patients do not progress to severe disease the overall case fatality rate per infected individual is low, but hospitals in areas with significant community transmission have experienced a major increase in the number of hospitalised pneumonia patients, and the frequency of severe disease in hospitalised patients can be as high as 30%.[2-4] The progression from prodrome (usually fever, fatigue and cough) to severe pneumonia requiring oxygen support or mechanical ventilation often takes one to two weeks after the onset of symptoms.[2] The kinetics of viral replication in the respiratory tract are not well characterized, but this relatively slow progression provides a potential time window in which antiviral therapies could influence the course of disease.

1.2 Treatment Options

1.2.1 Main randomisation

There are currently no approved treatments for COVID-19. This protocol allows reliable assessment of the effects of multiple different treatments (including re-purposed and novel drugs) on major outcomes in COVID-19. All patients will receive usual care for the participating hospital.

From version 6.0 of the protocol, a factorial design will be used such that eligible and consenting participants may be randomised to one of the treatment arms in Randomisation A and, simultaneously, to one of the treatment arms in Randomisation B.

Randomisation part A: Eligible patients will be randomly allocated between the following treatment arms (although not all arms may be available at any one time):

- **No additional treatment:** There are currently no approved anti-viral or host-directed treatments for COVID-19.

- **Lopinavir-ritonavir:** Lopinavir is a human immunodeficiency virus 1 (HIV-1) protease inhibitor, which is combined with ritonavir to increase lopinavir's plasma half-life. Lopinavir-Ritonavir has shown activity against SARS and MERS CoVs.

- **Low dose corticosteroids:** Favourable immune response modulation by low-dose corticosteroids might help treat severe acute respiratory coronavirus infections, including COVID-19, SARS and MERS.

- **Hydroxychloroquine:** Hydroxychloroquine, a derivative of chloroquine, has been used for many decades to treat malaria and rheumatological diseases. It has antiviral activity against SARS-CoV-2 in cell culture.

- **Azithromycin:** Azithromycin is a macrolide antibiotic with immunomodulatory properties that has shown benefit in inflammatory lung disease.

Randomisation part B: Simultaneously, eligible patients will be randomly allocated between the following treatment arms (provided there are no contraindications and the appropriate consent has been given):

- **No additional treatment:** There are currently no approved anti-viral or host-directed treatments for COVID-19.

- **Convalescent plasma:** Plasma from patients who have recovered from SARS-CoV-2 infection may contain antibodies that can bind to and neutralise the virus. Infusion of convalescent plasma containing high concentrations of neutralising antibody may accelerate clearance of the virus and clinical improvement.

Further details on each of these treatment options is provided in Appendix 1 (see section 8.1).

1.2.2 Second randomisation for patients with progressive COVID-19

Severe COVID-19 is associated with release of pro-inflammatory cytokines, such as IL-1, IL-6 and TNFα, and other markers of systemic inflammation including ferritin and C-reactive protein.[3,5,6] There is a possibility that this response may cause or exacerbate lung injury, leading to life-threatening disease.

Participants with progressive COVID-19 (as evidenced by hypoxia and an inflammatory state) may undergo an optional second randomisation between the following treatment arms:

- **No additional treatment:** There are currently no approved immunomodulatory or other host-directed treatments to prevent the progression of COVID-19.

- **Tocilizumab:** Tocilizumab is an interleukin-6 (IL-6) receptor antibody, which blocks a component of the immune response that may drive progression to ARDS.

Modifications to the number of treatment arms: Other arms can be added to the first or second randomisation if evidence emerges that there are suitable candidate therapeutics. Conversely, in some patient populations, not all trial arms are appropriate (e.g. due to contraindications based on co-morbid conditions or concomitant medication); in some hospitals, not all treatment arms will be available (e.g. due to manufacturing and supply shortages); and at some times, not all treatment arms will be active (e.g. due to lack of relevant approvals and contractual agreements). The Trial Steering Committee may elect to pause one or more of the arms in order to increase trial efficiency during a fluctuating epidemic. In any of these situations, randomisation will be between fewer arms.

1.3 Design Considerations

The RECOVERY Protocol describes an overarching trial design to provide reliable evidence on the efficacy of candidate therapies for suspected or confirmed COVID-19 infection in hospitalised patients receiving usual standard of care.

There are no known treatments for COVID-19. The anticipated scale of the epidemic is such that hospitals, and particularly intensive care facilities, may be massively overstretched. Under some models of pandemic spread, up to 50% of the adult population may fall sick over a period of 8-12 weeks, of whom around 10% may require hospitalisation. This would involve about 2 million hospital admissions. In this situation, even treatments with only a moderate impact on survival or on hospital resources could be worthwhile. Therefore, the focus of RECOVERY is the impact of candidate treatments on mortality and on the need for hospitalisation or ventilation.

Critically, the trial is designed to minimise the burden on front-line hospital staff working within an overstretched care system during a major epidemic. Eligibility criteria are therefore simple and trial processes (including paperwork) are minimised.

The protocol is deliberately flexible so that it is suitable for a wide range of settings, allowing:

- a broad range of patients to be enrolled in large numbers;
- randomisation between only those treatment arms that are *both* available at the hospital *and* not believed by the enrolling doctor to be contraindicated (e.g. by particular co-morbid conditions or concomitant medications);
- treatment arms to be added or removed according to the emerging evidence; and
- additional sub-studies may be added to provide more detailed information on side effects or sub-categorisation of patient types but these are not the primary objective and are not required for participation.

In a cohort of 191 hospitalised COVID-19 patients with a completed outcome, the median time from illness onset to discharge was 22·0 days (IQR 18·0–25·0) and the median time to death was 18·5 days (15·0–22·0). Thirty-two patients (17%) required invasive mechanical ventilation and the median time from onset to mechanical ventilation was 14.5 days. Therefore, early endpoint assessment, such as 28 days after the main randomisation, is likely to provide largely complete outcome data and will permit early assessment of treatment efficacy and safety.[7]

2 DESIGN AND PROCEDURES

2.1 Eligibility

Patients are eligible for the study if all of the following are true:

(i) Hospitalised
(ii) SARS-CoV-2 infection (clinically suspected[a] or laboratory confirmed)[b]
(iii) No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in the trial

In addition, if the attending clinician believes that there is a specific contra-indication to one of the active drug treatment arms (see Appendix 2; section 8.2 and Appendix 3; section 9.3 for children) or that the patient should definitely be receiving one of the active drug treatment arms then that arm will not be available for randomisation for that patient. For patients who lack capacity, an advanced directive or behaviour that clearly indicates that they would not wish to participate in the trial would be considered sufficient reason to exclude them from the trial.

2.2 Consent

Informed consent should be obtained from each patient 16 years and over before enrolment into the study. However, if the patient lacks capacity to give consent due to the severity of their medical condition (e.g. acute respiratory failure or need for immediate ventilation) or prior disease, then consent may be obtained from a relative acting as the patient's legally designated representative or independent doctor. Further consent will then be sought with the patient if they recover sufficiently. For children aged <16 years old consent will be sought from their parents or legal guardian. Where possible, children aged between 10-15 years old will also be asked for assent. Children aged ≥16 years old will asked for consent as for adults. Witnessed consent may be obtained over the telephone or web video link if hospital visiting rules or parental infection mean a parent/guardian cannot be physically present.

Due to the poor outcomes in COVID-19 patients who require ventilation (>90% mortality in one cohort[7]), patients who lack capacity to consent due to severe disease (e.g. needs ventilation), and for whom a relative to act as the legally designated representative is not immediately available, randomisation and consequent treatment will proceed with consent

[a] In general, SARS-CoV-2 infection should be suspected when a patient presents with (i) typical symptoms (e.g. influenza-like illness with fever and muscle pain, or respiratory illness with cough and shortness of breath); and (ii) compatible chest X-ray findings (consolidation or ground-glass shadowing); and (iii) alternative causes have been considered unlikely or excluded (e.g. heart failure, influenza). However, the diagnosis remains a clinical one based on the opinion of the managing doctor.
[b] A small number of children (age <18 years old) present with atypical features, including a hyperinflammatory state and evidence of single or multi-organ dysfunction. Some do not have significant lung involvement.
(see: https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf)

provided by a treating clinician (independent of the clinician seeking to enrol the patient) who will act as the legally designated representative. Consent will then be obtained from the patient's personal legally designated representative (or directly from the patient if they recover promptly) at the earliest opportunity.

2.3 Baseline information

The following information will be recorded on the web-based form by the attending clinician or delegate:

- Patient details (e.g. name, NHS number, date of birth, sex)
- Clinician details (e.g. name)
- COVID-19 symptom onset date
- COVID-19 severity as assessed by need for supplemental oxygen or ventilation/extracorporeal membrane oxygenation (ECMO)
- Major comorbidity (e.g. heart disease, diabetes, chronic lung disease) and pregnancy
- Date of hospitalisation
- Contraindication to the study treatment regimens (in the opinion of the attending clinician)
- Willingness to receive a blood product
- Name of person completing the form

The person completing the form will then be asked to confirm that they wish to randomise the patient and will then be required to enter their name and e-mail address.

2.4 Main randomisation

In addition to receiving usual care, eligible patients will be allocated using a central web-based randomisation service (without stratification or minimisation). From version 6.0 of the protocol, a factorial design will be used such that eligible patients are randomised to one of the treatment arms in Randomisation A and, simultaneously, to one of the treatment arms in Randomisation B.

2.4.1 Main randomisation part A:

Eligible patients will be randomised to one of the arms listed below. The doses in this section are for adults. Please see Appendix 3 for paediatric dosing. Study treatments do not need to be continued after discharge from hospital.

- **No additional treatment**

- **Lopinavir 400mg-Ritonavir 100mg** by mouth (or nasogastric tube) every 12 hours for 10 days.

- **Corticosteroid** in the form of dexamethasone administered as an oral (liquid or tablets) or intravenous preparation 6 mg once daily for 10 days. In pregnancy or breastfeeding women, prednisolone 40 mg administered by mouth (or intravenous hydrocortisone 80 mg twice daily) should be used instead of dexamethasone.

(Note: It is permitted to switch between the two routes of administration according to clinical circumstances.)

- **Hydroxychloroquine** by mouth for a total of 10 days as follows:

Timing	Dose
Initial	800 mg
6 hours after initial dose	800 mg
12 hours after initial dose	400 mg
24 hours after initial dose	400 mg
Every 12 hours thereafter for 9 days	400 mg

- **Azithromycin 500mg** by mouth (or nasogastric tube) or intravenously once daily for 10 days.

For randomisation part A, the randomisation program will allocate patients in a ratio of 2:1 between the no additional treatment arm and each of the other arms available. Hence if 5 arms are available, then the randomisation will be in the ratio 2:1:1:1:1. If one or more of the active drug treatments is not available at the hospital or is believed, by the attending clinician, to be contraindicated (or definitely indicated) for the specific patient, then this fact will be recorded via the web-based form prior to randomisation; random allocation will then be between the remaining arms (i.e. in a 2:1:1:1, 2:1:1 or 2:1 ratio).

2.4.2 Main randomisation part B:

Eligible patients may be randomised to one of the arms listed below. The doses in this section are for adults. Please see Appendix 3 for paediatric dosing.

- **No additional treatment**

- **Convalescent plasma**

  Single unit of ABO compatible convalescent plasma (275mls +/- 75 mls) intravenous per day on study days 1 (as soon as possible after randomisation) and 2 (with a minimum of 12 hour interval between 1st and 2nd units). ABO identical plasma is preferred if available. The second transfusion should not be given if patient has a suspected serious adverse reaction during or after the first transfusion.

For randomisation part B, the randomisation program will allocate patients in a ratio of 1:1 between each of the arms. If the active treatment is not available at the hospital, the patient does not consent to receive convalescent plasma, or is believed, by the attending clinician, to be contraindicated for the specific patient, then this fact will be recorded via the web-based form and the patient will be excluded from Randomisation part B.

2.5 Administration of allocated treatment

The details of the allocated study treatments will be displayed on the screen and can be printed or downloaded. The hospital clinicians are responsible for administration of the allocated treatments. The patient's own doctors are free to modify or stop study treatments

if they feel it is in the best interests of the patient without the need for the patient to withdraw from the study (see section 2.9). This study is being conducted within hospitals. Therefore use of medication will be subject to standard medication reviews (typically within 48 hours of enrolment) which will guide modifications to both the study treatment and use of concomitant medication (e.g. in the case of potential drug interactions).

Note: NHS guidelines require patients to have **two** separate blood samples taken for Group and Screen prior to administration of blood products. Each sample is approximately 5 mL and both need to be taken at any time between admission to hospital and receipt of the first plasma transfusion (as the laboratory will not issue plasma without both samples). The participant's blood group is identified to ensure that blood group-compatible plasma is given and this information would be available to the participant if they wish. Such tests may be required as part of the routine care of the participant if the managing team wish to consider using blood products and samples will be stored, retained and destroyed as per trust standard procedures and protocols.

2.6 Second randomisation for patients with progressive COVID-19

Patients enrolled in the RECOVERY trial and with clinical evidence of a hyper-inflammatory state may be considered for a second randomisation if they meet the following criteria:

(i) Randomised into the RECOVERY trial no more than 21 days ago
(ii) Clinical evidence of progressive COVID-19:
    a. oxygen saturation <92% on room air or requiring oxygen
    (or in children (age <18 years), significant systemic disease with persistent pyrexia, with or without evidence of respiratory involvement)[c]; and
    b. C-reactive protein ≥75 mg/L
(iii) No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in this aspect of the RECOVERY trial.
    (Note: Pregnancy and breastfeeding are not specific exclusion criteria.)

Note: Participants may undergo this second randomisation at any point after being first randomised, provided they meet the above criteria, and thus may receive up to three study treatments (one each from Main randomisation parts A and B, plus one from the second randomisation). For some participants the second randomisation may be immediately after the first but for others it may occur a few hours or days later, if and when they deteriorate. Those transferred from the Trust at which they were originally enrolled in the trial will be ineligible for the second randomisation.

The following information will be recorded (on the web-based form) by the attending clinician or delegate:

[c] A small number of children (age <18 years) present with atypical features, including a hyperinflammatory state and evidence of single or multi-organ dysfunction. Some do not have significant lung involvement.
(see: https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf)

- Patient details (e.g. name, NHS number, date of birth, sex)
- Clinician details (e.g. name)
- COVID-19 severity as assessed by need for supplemental oxygen or ventilation/ECMO
- Markers of progressive COVID-19 (including oxygen saturation, C-reactive protein)
- Contraindication to the study drug treatments (in the opinion of the attending clinician)
- Name of person completing the form

The person completing the form will then be asked to confirm that they wish to randomise the patient and will then be required to enter their own name and e-mail address.

Eligible participants may be randomised between the following treatment arms:

- **No additional treatment:** There are currently no approved anti-viral or host-directed treatments for COVID-19.

- **Tocilizumab** by intravenous infusion with the dose determined by body weight:

Weight*	Dose
>40 and ≤65 kg	400 mg
>65 and ≤90 kg	600 mg
>90 kg	800 mg

* for lower weights, dosing should be 8 mg/kg (see Appendix 3 for paediatric dosing)
(Note: body weight may be estimated if it is impractical to weigh the patient)

Tocilizumab should be given as a single intravenous infusion over 60 minutes in 100ml sodium chloride 0.9%. A second dose may be given ≥12 and <24 hours later if, in the opinion of the attending clinician, the patient's condition has not improved.

The randomisation program will allocate patients in a ratio of 1:1 between the arms being evaluated in the second randomisation. Participants should receive standard management (including blood tests such as liver function tests and full blood count) according to their clinical need.

2.7 Collecting follow-up information

The following information will be ascertained at the time of death or discharge or at 28 days after first randomisation (whichever is sooner):

- Vital status (alive / dead, with date and presumed cause of death, if appropriate)
- Hospitalisation status (inpatient / discharged, with date of discharge, if appropriate)
- Use of ventilation (with days of use and type, if appropriate)
- Use of renal dialysis or haemofiltration
- Documented new major cardiac arrhythmia (including atrial and ventricular arrhythmias)
- Use of any medications included in the RECOVERY trial protocol (including drugs in the same class)

This information will be obtained and entered into the web-based IT system by a member of the hospital clinical or research staff.

Follow-up information is to be collected on all study participants, irrespective of whether or not they complete the scheduled course of allocated study treatment. Study staff will seek follow-up information through various means including medical staff, reviewing information from medical notes, routine healthcare systems, and registries.

2.7.1 Additional assessment of safety of convalescent plasma

For the first 200 participants in Main Randomisation part B (no additional treatment vs. convalescent plasma), the following information will be collected on the following events occurring within the first 72 hours after randomisation:

- Sudden worsening in respiratory status
- Severe allergic reaction
- Temperature >39^{o}C or ≥2^{o}C rise above baseline
- Sudden hypotension, defined as either (i) sudden drop in systolic blood pressure of ≥30 mmHg with systolic blood pressure ≤80 mmHg; or (ii) requiring urgent medical attention
- Clinical haemolysis, defined as fall in haemoglobin plus one or more of the following: rise in lactate dehydrogenase (LDH), rise in bilirubin, positive direct antiglobulin test (DAT), or positive crossmatch.

The Data Monitoring Committee will review unblinded information on these outcomes and advise if, in their view, the collection of such information should be extended to more participants.

In addition, Serious Hazards Of Transfusion (SHOT) reporting will be conducted for all patients receiving convalescent plasma for the full duration of the study (see section 4.1).

2.8 Duration of follow-up

All randomised participants are to be followed up until death, discharge from hospital or 28 days after first randomisation (whichever is sooner). It is recognised that in the setting of this trial, there may be some variability in exactly how many days after randomisation, information on disease status is collected. This is acceptable and will be taken account of in the analyses and interpretation of results, the principle being that some information about post-randomisation disease status is better than none.

Longer term (up to 10 years) follow-up will be sought through linkage to electronic healthcare records and medical databases including those held by NHS Digital, Public Health England and equivalent bodies, and to relevant research databases (e.g. UK Biobank, Genomics England).

2.9 Withdrawal of consent

A decision by a participant (or their parent/guardian) that they no longer wish to continue receiving study treatment should **not** be considered to be a withdrawal of consent for follow-up. However, participants (or their parent/guardian) are free to withdraw consent for some or all aspects of the study at any time if they wish to do so. In accordance with

regulatory guidance, de-identified data that have already been collected and incorporated in the study database will continue to be used (and any identifiable data will be destroyed).

For participants who lack capacity, if their legal representative withdraws consent for treatment or methods of follow-up then these activities would cease.

3 STATISTICAL ANALYSIS

All analyses for reports, presentations and publications will be prepared by the coordinating centre at the Nuffield Department of Population Health, University of Oxford. A more detailed statistical analysis plan will be developed by the investigators and published on the study website whilst still blind to any analyses of aggregated data on study outcomes by treatment allocation.

3.1 Outcomes

For each pairwise comparison with the 'no additional treatment' arm, the **primary objective** is to provide reliable estimates of the effect of study treatments on all-cause mortality at 28 days after first randomisation (with subsidiary analyses of cause of death and of death at various timepoints following discharge).

The **secondary objectives** are to assess the effects of study treatments on duration of hospital stay; the need for (and duration of) ventilation; and, among patients not on ventilation at baseline, the composite endpoint of death or need for mechanical ventilation or ECMO.

Other objectives include the assessment of the effects of study treatments on the need for renal replacement therapy and new major cardiac arrhythmias.

Study outcomes will be assessed based on data recorded up to 28 days and up to 6 months after the main randomisation.

Data from routine healthcare records (including linkage to medical databases held by organisations such as NHS Digital) and from relevant research studies (such as UK Biobank and Genomics England) will allow subsidiary analyses of the effect of the study treatments on particular non-fatal events (e.g. ascertained through linkage to Hospital Episode Statistics), the influence of pre-existing major co-morbidity (e.g. diabetes, heart disease, lung disease, hepatic insufficiency, severe depression, severe kidney impairment, immunosuppression), and longer-term outcomes as well as in particular sub-categories of patient (e.g. by genotype, pregnancy).

3.2 Methods of analysis

For all outcomes, comparisons will be made between all participants randomised to the different treatment arms, irrespective of whether they received their allocated treatment ("intention-to-treat" analyses).

For time-to-event analyses, each treatment group will be compared with the no additional treatment group using the log-rank test. Kaplan-Meier estimates for the time to event will

also be plotted (with associated log-rank p-values). The log-rank 'observed minus expected' statistic (and its variance) will also be used to estimate the average event rate ratio (and its confidence interval) for those allocated to each treatment group versus the no additional treatment group. For binary outcomes where the timing is unknown, the risk ratio and absolute risk difference will be calculated with confidence intervals and p-value reported. For the primary outcome (death within 28 days of first randomisation), discharge alive before 28 days will assume safety from the event (unless there is additional data confirming otherwise).

Pairwise comparisons within each randomisation will be made between each treatment arm and the no additional treatment arm (reference group) in that particular randomisation (main randomisation phase A, main randomisation phase B, and second randomisation). However, since not all treatments may be available or suitable for all patients, those in the no additional treatment arm will only be included in a given comparison if, at the point of their randomisation, they *could* alternatively have been randomised to the active treatment of interest. Adjustment for multiple treatment comparisions due to the multi-arm design will be made. All p-values will be 2-sided.

Pre-specified subgroup analysis (e.g., disease severity; time since onset of symptoms; sex; age group) will be conducted for the primary outcome using the statistical test for interaction (or test for trend where appropriate),

Further details will be fully described in the Statistical Analysis Plan.

4 DATA AND SAFETY MONITORING

4.1 Recording Suspected Serious Adverse Reactions

The focus is on those events that, based on a single case, are highly likely to be related to the study medication. Examples include anaphylaxis, Stevens Johnson Syndrome, or bone marrow failure, where there is no other plausible explanation.

Any Serious Adverse Event[d] that is believed with a reasonable probability to be due to one of the study treatments will be considered a Suspected Serious Adverse Reaction (SSAR). In making this assessment, there should be consideration of the probability of an alternative cause (for example, COVID-19 itself or some other condition preceding randomisation), the timing of the event with respect to study treatment, the response to withdrawal of the study treatment, and (where appropriate) the response to subsequent re-challenge.

[d] Serious Adverse Events are defined as those adverse events that result in death; are life-threatening; require in-patient hospitalisation or prolongation of existing hospitalisation; result in persistent or significant disability or incapacity; result in congenital anomaly or birth defect; or are important medical events in the opinion of the responsible investigator (that is, not life-threatening or resulting in hospitalisation, but may jeopardise the participant or require intervention to prevent one or other of the outcomes listed above).

All SSARs should be reported by telephone to the Central Coordinating Office and recorded on the study IT system immediately.

Suspected serious transfusion reactions in patients who receive convalescent plasma should additionally be reported to Serious Hazards of Transfusions (SHOT) and through the MHRA Serious Adverse Blood Reactions and Events (SABRE) system.[e]

4.2 Central assessment and onward reporting of SUSARs

Clinicians at the Central Coordinating Office are responsible for expedited review of reports of SSARs received. Additional information (including the reason for considering it both serious and related, and relevant medical and medication history) will be sought.

The focus of SUSAR reporting will be on those events that, based on a single case, are highly likely to be related to the study medication. To this end, anticipated events that are either efficacy endpoints, consequences of the underlying disease, or common in the study population will be exempted from expedited reporting. Thus the following events will be exempted from expedited reporting:

(i) Events which are the consequence of COVID-19; and
(ii) Common events which are the consequence of conditions preceding randomisation.

Any SSARs that are not exempt will be reviewed by a Central Coordinating Office clinician and an assessment made of whether the event is “expected” or not (assessed against the relevant Summary of Product Characteristics or Investigator Brochure). Any SSARs that are not expected would be considered a Suspected Unexpected Serious Adverse Reaction (SUSAR).

All confirmed SUSARs will be reported to the Chair of the DMC and to relevant regulatory authorities, ethics committees, and investigators in an expedited manner in accordance with regulatory requirements.

4.3 Recording other Adverse Events

In addition to recording Suspected Serious Adverse Reactions (see section 4.1), information will be collected on all deaths and efforts will be made to ascertain the underlying cause. Other serious or non-serious adverse events will not be recorded. It is anticipated that for some sub-studies, more detailed information on adverse events (e.g. through linkage to medical databases) or on other effects of the treatment (e.g. laboratory or radiological features) will be recorded and analysed but this is not a requirement of the core protocol.

[e] https://www.shotuk.org/reporting/

4.4 Role of the Data Monitoring Committee (DMC)

During the study, interim analyses of all study data will be supplied in strict confidence to the independent DMC. The DMC will request such analyses at a frequency relevant to the emerging data from this and other studies.

The DMC will independently evaluate these analyses and any other information considered relevant. The DMC will determine if, in their view, the randomised comparisons in the study have provided evidence on mortality that is strong enough (with a range of uncertainty around the results that is narrow enough) to affect national and global treatment strategies. In such a circumstance, the DMC will inform the Trial Steering Committee who will make the results available to the public and amend the trial arms accordingly. Unless this happens, the Steering Committee, Chief Investigator, study staff, investigators, study participants, funders and other partners will remain blind to the interim results until 28 days after the last patient has been randomised for a particular intervention arm (at which point analyses may be conducted comparing that arm with the no additional treatment arm).

The DMC will review the safety and efficacy analyses among children (age <18 years) both separately and combined with the adult data. As described in section 2.7.1, the DMC will advise if collection of information relating to the safety of convalescent plasma should be extended beyond the first 200 patients enrolled to Main Randomisation phase B (no additional treatment *vs.* convalescent plasma).

4.5 Blinding

This is an open-label study. However, while the study is in progress, access to tabular results of study outcomes by allocated treatment allocation will not be available to the research team, patients, or members of the Steering Committee (unless the DMC advises otherwise).

5 QUALITY MANAGEMENT

5.1 Quality By Design Principles

In accordance with the principles of Good Clinical Practice and the recommendations and guidelines issued by regulatory agencies, the design, conduct and analysis of this trial is focussed on issues that might have a material impact on the wellbeing and safety of study participants (hospitalised patients with suspected or confirmed SARS-CoV-2 infection) and the reliability of the results that would inform the care for future patients.

The critical factors that influence the ability to deliver these quality objectives are:

- to minimise the burden on busy clinicians working in an overstretched hospital during a major epidemic
- to ensure that suitable patients have access to the trial medication without impacting or delaying other aspects of their emergency care

- to provide information on the study to patients and clinicians in a timely and readily digestible fashion but without impacting adversely on other aspects of the trial or the patient's care
- to allow individual clinicians to use their judgement about whether any of the treatment arms are not suitable for the patient
- to collect comprehensive information on the mortality and disease status

In assessing any risks to patient safety and well-being, a key principle is that of proportionality. Risks associated with participation in the trial must be considered in the context of usual care. At present, there are no proven treatments for COVID-19, basic hospital care (staffing, beds, ventilatory support) may well be overstretched, and mortality for hospitalised patients may be around 10% (or more in those who are older or have significant co-morbidity).

5.2 Training and monitoring

The focus will be on those factors that are critical to quality (i.e. the safety of the participants and the reliability of the trial results). Remedial actions would focus on issues with the potential to have a substantial impact on the safety of the study participants or the reliability of the results.

The study will be conducted in accordance with the principles of International Conference on Harmonisation Guidelines for Good Clinical Research Practice (ICH-GCP) and relevant local, national and international regulations. Any serious breach of GCP in the conduct of the clinical trial will be handled in accordance with regulatory requirements. Prior to initiation of the study at each Local Clinical Centre (LCC), the Central Coordinating Office (CCO) will confirm that the LCC has adequate facilities and resources to carry out the study. LCC lead investigators and study staff will be provided with training materials.

In the context of this epidemic, visits to hospital sites is generally not appropriate as they could increase the risks of spreading infection, and in the context of this trial they generally would not influence the reliability of the trial results or the well-being of the participants. In exceptional circumstances, the CCO may arrange monitoring visits to LCCs as considered appropriate based on perceived training needs and the results of central statistical monitoring of study data.[8,9] The purpose of such visits will be to ensure that the study is being conducted in accordance with the protocol, to help LCC staff to resolve any local problems, and to provide extra training focussed on specific needs. No routine source data verification will take place.

Training of laboratory and transfusion staff and initiation of convalescent plasma delivery will be performed by NHS Blood and Transplant Clinical Trials Unit.

5.3 Data management

LCC clinic staff will use the bespoke study web-based applications for study management and to record participant data (including case report forms) in accordance with the protocol. Data will be held in central databases located at the CCO or on secure cloud servers. In some circumstances (e.g. where there is difficulty accessing the internet or necessary IT equipment), paper case report forms may be required with subsequent data

entry by either LCC or CCO staff. Although data entry should be mindful of the desire to maintain integrity and audit trails, in the circumstances of this epidemic, the priority is on the timely entry of data that is sufficient to support reliable analysis and interpretation about treatment effects. CCO staff will use be responsible for provision of the relevant web-based applications and for generation of data extracts for analyses.

All data access will be controlled by unique usernames and passwords, and any changes to data will require the user to enter their username and password as an electronic signature in accordance with regulatory requirements.[10] Staff will have access restricted to the functionality and data that are appropriate for their role in the study.

5.4 Source documents and archiving

Source documents for the study constitute the records held in the study main database. These will be retained for at least 25 years from the completion of the study. Identifiable data will be retained only for so long as it is required to maintain linkage with routine data sources (see section 2.8), with the exception of children for whom such data must be stored until they reach 21 years old (due to the statute of limitations). The sponsor and regulatory agencies will have the right to conduct confidential audits of such records in the CCO and LCCs (but should mindful of the workload facing participating hospitals and the infection control requirements during this epidemic).

6 OPERATIONAL AND ADMINISTRATIVE DETAILS

6.1 Sponsor and coordination

The University of Oxford will act as the trial Sponsor. The trial will be coordinated by a Central Coordinating Office within the Nuffield Department of Population Health staffed by members of the two registered clinical trials units – the Clinical Trial Service Unit and the National Perinatal Epidemiology Unit Clinical Trials Unit. The data will be collected, analysed and published independently of the source of funding.

6.2 Funding

This study is supported by a grant to the University of Oxford from UK Research and Innovation/National Institute for Health Research (NIHR) and by core funding provided by NIHR Oxford Biomedical Research Centre, the Wellcome Trust, the Bill and Melinda Gates Foundation, Health Data Research UK, and the Medical Research Council Population Health Research Unit, and NIHR Clinical Trials Unit Support Funding.

6.3 Indemnity

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

6.4 Local Clinical Centres

The study will be conducted at multiple hospitals (Local Clinical Centres) within the UK. At each LCC, a lead investigator will be responsible for trial activities but much of the work will be carried out by medical staff attending patients with COVID-19 within the hospital and by hospital research nurses, medical students and other staff with appropriate education, training, and experience. Where LCCs plan to recruit children the principal investigator will co-opt support from a local paediatrician and/or neonatologists to oversee the management of children and infants in the trial.

6.5 Supply of study treatments

For licensed treatments (e.g. lopinavir-ritonavir, corticosteroids, tocilizumab) all aspects of treatment supply, storage, and management will be in accordance with standard local policy and practice for prescription medications. Treatment issue to randomised participants will be by prescription.

For unlicensed treatments, manufacture, packaging and delivery will be the responsibility of the pharmaceutical company and Department of Health and Social Care. Treatment issue to randomised participants will be in accordance with local practice (and may be in line with the processes required for routine prescriptions or compassionate use).

For convalescent plasma, manufacture, packaging, and delivery will be the responsibility of the relevant UK Blood Service (NHS Blood and Transplant for England, Welsh Blood Service for Wales, Scottish National Blood Transfusion Service for Scotland, and the Northern Ireland Blood Transfusion Service for Northern Ireland). Convalescent plasma will be labelled in accordance with regulatory requirements and the unit will be issued to the ward for a named patient in a bag marked for clinical trial use only. Treatment issue to randomised participants will be by prescription.

Study treatments will not be labelled beyond other than as required for routine clinical use. They will be stored alongside other routine medications with no additional monitoring. No accountability records will be kept beyond those used for routine prescriptions.

6.6 End of trial

The end of the scheduled treatment phase is defined as the date of the last follow-up visit of the last participant. In the UK, it is intended to extend follow-up for a year or more beyond the final study visit through linkage to routine medical records and central medical databases. The end of the study is the date of the final data extraction from NHS Digital (anticipated to be 10 years after the last patient is enrolled).

6.7 Publications and reports

The Steering Committee will be responsible for drafting the main reports from the study and for review of any other reports. In general, papers initiated by the Steering Committee (including the primary manuscript) will be written in the name of the RECOVERY Collaborative Group, with individual investigators named personally at the end of the report (or, to comply with journal requirements, in web-based material posted with the report).

The Steering Committee will also establish a process by which proposals for additional publications (including from independent external researchers) are considered by the Steering Committee. The Steering Committee will facilitate the use of the study data and approval will not be unreasonably withheld. However, the Steering Committee will need to be satisfied that any proposed publication is of high quality, honours the commitments made to the study participants in the consent documentation and ethical approvals, and is compliant with relevant legal and regulatory requirements (e.g. relating to data protection and privacy). The Steering Committee will have the right to review and comment on any draft manuscripts prior to publication.

6.8 Substudies

Proposals for substudies must be approved by the Steering Committee and by the relevant ethics committee and competent authorities (where required) as a substantial amendment or separate study before they begin. In considering such proposals, the Steering Committee will need to be satisfied that the proposed substudy is worthwhile and will not compromise the main study in any way (e.g. by impairing recruitment or the ability of the participating hospitals to provide care to all patients under their care).

7 VERSION HISTORY

Version number	Date	Brief Description of Changes
1.0	13-Mar-2020	Initial version
2.0	21-Mar-2020	Addition of hydroxychloroquine. Administrative changes and other clarifications.
3.0	07-Apr-2020	Extension of eligibility to those with suspected COVID-19 Addition of azithromycin arm. Addition of inclusion of adults who lack permanently lack capacity. Change to primary outcome from in-hospital death to death within 28 days of randomization.
4.0	14-Apr-2020	Addition of second randomisation to tocilizumab vs. standard of care among patients with progressive COVID-19.
5.0	24-Apr-2020	Addition of children to study population.
6.0	14-May-2020	Addition of convalescent plasma

8 APPENDICES

8.1 Appendix 1: Information about the treatment arms

All patients will receive usual care in the participating hospital.

No additional treatment: There are no proven therapies for COVID-19.

Lopinavir-ritonavir: Lopinavir is a human immunodeficiency virus 1 (HIV-1) protease inhibitor, which is combined with ritonavir to increase lopinavir's plasma half-life. It is licensed in adults and children from the age of 14 days (2 years in Scotland). It has been widely used in pregnant women.[11] Lopinavir has in vitro inhibitory activity against SARS coronavirus (SARS-CoV) and MERS-CoV.[12-14 15] In common marmosets infected with MERS-CoV, animals treated with lopinavir/ritonavir had improved clinical, radiological, and pathological outcomes and reduced viral loads compared with untreated animals.[16] In one single-center, open-label study of the addition of lopinavir 400mg/ritonavir 100mg to ribavirin and corticosteroids in SARS patients the risk of adverse clinical outcomes (acute respiratory distress syndrome [ARDS] or death) was significantly lower (2.4% v 28.8%, p<0.001) compared to a historical control group.[12]

The most common short-term side effects in adults are diarrhoea, nausea, and vomiting. It must not be used by patients with severe liver disease. It should not be co-administered with medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events (see Summary of Product Characteristics). Storage should be as per conditions in the Summary of Product Characteristics.

Dexamethasone: Favourable modulation of the immune response is considered one of the possible mechanisms by which corticosteroids might be beneficial in the treatment of severe acute respiratory coronavirus infections, including COVID-19, SARS and MERS. Common to severe cases of these infections is the presence of hypercytokinemia (a cytokine 'storm') and development of acute lung injury or acute respiratory distress syndrome (ARDS).[17-20] Pathologically, diffuse alveolar damage is found in patients who die from these infections.[21] A growing volume of clinical trial data from patients with severe community acquired pneumonia, ARDS and septic shock suggest benefit from low-to-moderate dose corticosteroids in relation to mortality and length of stay.[22-24]

In trials of low-to-moderate doses of corticosteroids, the main adverse effect has been hyperglycaemia.[23,25] A systematic review of (mainly low-dose) corticosteroid trials in severe sepsis and septic shock did not identify any increased risk of gastroduodenal bleeding, superinfection or neuromuscular weakness; an association with an increased risk of hyperglycaemia (RR 1.16, 95% CI 1.07 to 1.25) and hypernatraemia (RR 1.61, 95% CI 1.26 to 2.06) was noted.[26] Dexamethasone has a) minimal mineralocorticoid activity and does not affect sodium and water balance, thus avoiding potential problems with fluid retention which are not uncommon in severe viral pneumonitis/ARDS, and b) a comparatively long biological half-life of 36 to 54 hours enabling once a day dosing. In pregnancy, prednisolone 40 mg administered by mouth (or intravenous hydrocortisone 80

mg twice daily) should be used instead of dexamethasone. Storage should be as per conditions in the Summary of Product Characteristics.

Hydroxycholoroquine: Chloroquine (CQ), an antimalarial drug discovered in 1934 and introduced generally in 1947, is the drug to which humans have been most exposed, with an annual global consumption of hundreds of metric tonnes for over 50 years. It is inexpensive, simple to administer, and, at the appropriate doses, has an excellent safety profile in all age groups and has been the prophylactic drug of choice in pregnancy [27]. In addition to its antimalarial use both chloroquine and the closely related hydroxychloroquine (HCQ) are used in continuous daily dosing for rheumatoid arthritis, systemic and discoid lupus erythematosus and psoriatic arthritis. HCQ is reported to have better safety profile than CQ, better gastrointestinal tolerability, and less retinal toxicity [28].

CQ has significant antiviral activity against SARS-CoV-2 in cell culture (EC_{50} = 1.13 µM; CC_{50} > 100 µM, SI > 88.50), as it does for the related SARS-CoV-1 [29-32]. CQ blocks virus infection by increasing endosomal pH required for virus/ cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV.[31] In SARS-CoV-2 infected Vero cells, HCQ (EC_{50}=0.72 µM) has been reported to be more potent than CQ (EC_{50}=5.47 µM) [33], although Liu et al reported that CQ was more potent than HCQ.[34] These are relatively high levels by comparison with therapeutic exposures in the treatment of malaria but could be achieved with daily oral dosing. Chloroquine has complex pharmacokinetic properties and although the relationship between plasma concentrations and concentrations in respiratory epithelium is not known precisely, in rats the concentration in lung is between 124 and 748-fold that in plasma [35]. If active, HCQ concentrations in the human lung would be expected to exceed those required for the EC_{90} after an initial dose. There are preliminary reports emerging from China and France of clinical benefit in the treatment of COVID-19 infections [36,37].

The recommended adult dosing of chloroquine for treatment of non-falciparum malaria (BNF) is: Initially 620 mg, then 310 mg after 6-8 hours, then 310 mg daily for 2 days. This is equivalent to 930mg base in first 24 hours. This is a loading dose to ensure the necessary blood concentrations are achieved rapidly.

Hydroxychloroquine is very similar to chloroquine. It is used mainly to treat rheumatoid arthritis and other related conditions. The adult dose is usually 400-600mg per day (equivalent to 310 to 465 mg base). Sometimes 800mg per day is given.

The dose in RECOVERY is Hydroyxchloroquine (155mg base per 200 mg tablet):

Initial dose:	4 tablets
6 hours after initial dose:	4 tablets
12 hours after initial dose:	2 tablets
24 hours after initial dose:	2 tablets
Thereafter:	2 tablets every 12 hours for a total of 10 days

12x155mg = 1860mg base = in first 24 hours

So the loading dose in RECOVERY is twice the normal dose for treating malaria. However, this dose has been selected based on the available data of the IC_{50} for SARS-

CoV-2. The objective is to reach plasma concentrations that are inhibitory to the virus as soon as safely possible. The plasma concentrations that will result are at the higher end of those encountered during steady state treatment of rheumatoid arthritis. Given the significant mortality in patients hospitalised with COVID-19, this dose is felt to be justified. This is the schedule that has been adopted by the World Health Organisation. No dose adjustment is required for weight based on the doses defined in this protocol.

Azithromycin: Azithromycin is a macrolide antibiotic. In addition to their antimicrobial properties, the macrolide antibiotics are known to have immunomodulatory activity. The mechanism of immunomodulation includes decreased production of pro-inflammatory cytokines and inhibition of neutrophil activation.[38-40] Macrolides are widely used both in infectious pneumonia due to their antimicrobial activity and in chronic inflammatory lung disease due to the immunomodulatory effects.[41] Azithromycin is preferred over other macrolides because data suggest it has stronger immunomodulatory effects than other macrolides.[40]

The use of macrolides in influenza-associated pneumonia has been associated with a faster reduction in inflammatory cytokines and, in combination with naproxen, decreased mortality.[42-44] Observational studies in MERS-CoV have not demonstrated a mortality benefit of macrolide use.[45] Macrolides have not been evaluated in severe betacoronavirus infections in randomised controlled trials. The safety of macrolides is well established.

Tocilizumab is a monoclonal antibody that binds to the receptor for IL-6, blocking IL-6 signalling and reduces inflammation. Tocilizumab is licensed for use in patients with rheumatoid arthritis and for use in people aged at least 2 years with chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome.

Severe COVID-19 is associated with a hyper-inflammatory state with elevated ESR, C-reactive protein, D-dimers, lactate dehydrogenase, ferritin, and increased levels of pro-inflammatory cytokines including as IL-1 and IL-6.[4,46,47] _ENREF_3_46There have been published and unpublished (pre-print) case series reports of the successful treatment of COVID-19 patients with IL-6 inhibitors.[46,48] IL-6 inhibitors have not been evaluated for the treatment of COVID-19 in randomised controlled trials.

Convalescent plasma: Convalescent plasma treatment, containing high titres of polyclonal antibody, has been used to treat severe viral pneumonias. Many studies have been small or poorly controlled but have reported beneficial effects in avian influenza[49-51], influenza A (H1N1) infections in 1915-1917[52] and 2009/2010[53,54], and seasonal influenza B[55]. More relevant to SARS-CoV-2, a systematic review of convalescent plasma treatment in SARS-CoV infections in 2003 identified eight observational studies that all reported improved mortality associated with the use of convalescent plasma – infected patients received various amounts of convalescent plasma.[56] Recent studies in seasonal influenza A and in MERS-CoV highlight the importance of high avidity and high titre antibodies respectively.[57,58]

Convalescent plasma therapy had been given to at least 245 COVID-19 patients by the end of February 2020, and, according to a Chinese health official, 91 cases had shown improvement in clinical indicators and symptoms (http://www.xinhuanet.com/english/2020-02/28/c_138828177.htm). Five small case series (26 patients in total) have been published

that report the use of convalescent plasma in people with COVID-19 infection.[59-63] These studies have reported clinical and radiological improvements after treatment with convalescent plasma. However, these small uncontrolled studies have significant flaws and the reported effects are unreliable. Convalescent plasma is currently being tested in the REMAP-CAP trial among patients on intensive care units.

8.2 Appendix 2: Drug specific contraindications and cautions

Lopinavir/ritonavir

- Severe hepatic insufficiency*
- Co-administration with medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. This includes alfuzosin, ranolazine, amiodarone, dronaderone, fusidic acid, neratinib, venetoclax, colchicine, astemizole, terfenadine, lurasidone, pimozide, quetiapine, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, elbasvir/grazoprevir, ombitasvir/paritaprevir/ritonavir, lovastatin, simvastatin, lomitapide, avanafil, sildenafil, vardenafil, midazolam, triazolam, ciclosporin, tacrolimus, sirolimus, rivaroxaban and vorapaxar (See Summary of Product Characteristics for more detail). It may be appropriate to temporarily withhold such concomitant medication while the patient is receiving lopinavir/ritonavir. For patients receiving warfarin additional INR monitoring is advised.

Corticosteroid

- Known contra-indication to short-term low-dose corticosteroid.

Hydroxychloroquine

- Known prolonged QTc interval*
- Caution: Co-administration with medications that prolong the QT interval (e.g. macrolides, quinolones) is not an absolute contraindication, but it may be appropriate to check the QT interval by performing an ECG.

Azithromycin

- Known prolonged QTc interval*
- Co-administration with chloroquine or hydroxychloroquine
- Known hypersensitivity to macrolide antibiotic

Tocilizumab

- Known hypersensitivity to tocilizumab.
- Evidence of active TB infection
- Clear evidence of active bacterial, fungal, viral, or other infection (besides COVID-19)

(Note: Pregnancy and breastfeeding are not exclusion criteria.)

Convalescent plasma

- Known moderate or severe allergy to blood components *
- Not willing to receive a blood product*

* If these conditions are recorded on the baseline case report form, patients will be ineligible for randomisation to that arm of the study.

Note: This study is being conducted within hospitals. Therefore use of medication will be subject to standard medication reviews (typically within 48 hours of enrolment) and clinical assessments (including appropriate blood tests) which will guide modifications to both the study treatment and use of concomitant medication (e.g. in the case of potential drug interactions). The doctor may decide whether it is appropriate to stop such medications temporarily to allow the patient to complete the course of their assigned intervention.

Although all available data on use in pregnancy are reassuring, since the effect of some of the treatments on unborn babies is uncertain, female participants who are not already pregnant will be advised that they should not get pregnant within 3 months of the completion of trial treatment(s).

8.3 Appendix 3: Paediatric dosing information

Arm	Route	Weight [#]	Dose (Duration for all arms = 10 days or until discharge from hospital)
No additional treatment	-	-	-
Lopinavir-Ritonavir (Kaletra®) - 80/20mg in 1mL oral solution - 100/25mg tablet - 200/50mg tablet Tablets must NOT be crushed	Oral or Nasogastric	Preterm infants with a corrected gestation age of <42 weeks **or** neonates with postnatal age of < 14 days excluded	
		≤ 5 kg	0.2 mL/kg every 12 hours
		6 - 9 kg	1.5 mL every 12 hours
		10 - 13 kg	2 mL every 12 hours
		14 - 19 kg	2.5 mL every 12 hours or 200/50 mg every 12 hours
		20 - 24 kg	3 mL every 12 hours or 200/50 mg every 12 hours
		25 - 34 kg	4 mL every 12 hours or 300/75 mg every 12 hours
		≥ 35 kg	5 mL every 12 hours or 400/100 mg every 12 hours
Corticosteroid - Oral solution* - Tablet* - Soluble tablet* - Solution for injection* *various strengths available	Oral or Nasogastric or Intravenous	All Including pre-term neonates	**Hydrocortisone (IV) – additional option for Preterm infants with a corrected gestation age of <40 weeks:** 0.5 mg/kg every 12 hours for 7 days and then 0.5mg/kg once daily for 3 days or **Prednisolone (Oral/NG)**: 1 mg/kg once daily (max: 40 mg; doses can be rounded as per routine clinical practice) or **Methylprednisolone sodium succinate (IV):** 0.8 mg/kg once daily (max: 32 mg) or **Dexamethasone (Oral/NG/IV)**: 150 micrograms/kg (as base) once daily (max: 6 mg)

[#] Weight to be rounded to the nearest kg unless dosage expressed as mg/kg or mL/kg.

Arm	Route	Weight #	Dose (Duration for all arms = 10 days or until discharge from hospital)
Hydroxychloroquine sulfate Dose expressed as hydroxychloroquine sulfate - 200mg tablet (tablets may be crushed and dispersed in water to allow for aliquot dosing – see note below) **A baseline ECG (to check QTc interval) is recommended for paediatric patients randomised to hydroxychloroquine.**	Oral or Nasogastric	Infants with postnatal age of <180 days excluded	
		5 - 10 kg	Initial dose: 100 mg 6 hours after initial dose: 100 mg 12 hours after initial dose: 50 mg 24 hours after initial dose: 50 mg Then 50 mg every 12 hours
		11 - 20 kg	Initial dose: 200 mg 6 hours after initial dose: 200 mg 12 hours after initial dose: 100 mg 24 hours after initial dose: 100 mg Then 100 mg every 12 hours
		21 - 39 kg	Initial dose: 400 mg 6 hours after initial dose: 400 mg 12 hours after initial dose: 200 mg 24 hours after initial dose: 200 mg Then 200 mg every 12 hours
		≥ 40 kg	Initial dose: 800 mg 6 hours after initial dose: 800 mg 12 hours after initial dose: 400 mg 24 hours after initial dose: 400 mg Then 400 mg every 12 hours
Azithromycin - 40mg in 1mL oral suspension - 250mg tablet/capsule - 500mg tablet/capsule - 500mg powder for solution for infusion	Oral or Nasogastric or Intravenous	≤ 16 kg Including preterm neonates	10 mg/kg once daily
		17 - 25 kg	200 mg once daily
		26 - 35 kg	300 mg once daily
		36 - 45 kg	400 mg once daily
		≥ 46 kg	500 mg once daily
Convalescent Plasma	Intravenous		5 mL/kg of ABO compatible convalescent plasma intravenous up to standard adult dose of 275 mLs per day on study days 1 and 2. Minimum of 12 hour interval between 1st and 2nd units. Convalescent plasma for neonates and infants up to one year of age needs to be ordered on a named patient basis from the relevant National Blood Service to ensure the unit meets neonatal requirements. Data transfer storage and retention will be in line with NHSBT standard procedures and protocols.

Weight to be rounded to the nearest kg unless dosage expressed as mg/kg or mL/kg.

Note: Hydroxychloroquine oral solution is not available as authorised medicinal product in the EU. The European Directorate for the Quality of Medicines and the European Paediatric Formulary (PaedF) Working

Party have, in this exceptional situation, complied existing knowledge on paediatric formulations for hydroxychloroquine. As noted in their document, hydroxychloroquine sulfate is a highly soluble drug and it is expected that manipulation of the formulation will have minimal impact on bioavailability. The extemporaneously preparations described in literature is generally prepared by crushing of tablets and mixing with an aqueous base. On these basis and the urgent public health need of this trial, we propose that hydroxychloroquine tablets to be crushed and dispersed in water to allow for aliquot dosing in children if required**.**

Second stage randomisation (Patients < 1 year of age will NOT be eligible)

Arm	Route	Weight	Dose
No additional treatment	-	-	-
Tocilizumab	Intravenous	Infants < 1 year excluded	
		< 30 kg	12 mg/kg A second dose may be given ≥12 and ≤24 hours later if, in the opinion of the attending clinicians, the patient's condition has not improved.
		≥ 30 kg	8 mg/kg (max 800 mg) A second dose may be given ≥12 and ≤24 hours later if, in the opinion of the attending clinicians, the patient's condition has not improved.

8.4 Appendix 4: Organisational Structure and Responsibilities

Chief Investigator
The Chief Investigator has overall responsibility for:

(i) Design and conduct of the Study in collaboration with the Steering Committee;
(ii) Preparation of the Protocol and subsequent revisions;

Steering Committee
The Steering Committee (see Section 8.5 for list of members) is responsible for:

(i) Agreement of the final Protocol and the Data Analysis Plans;
(ii) Reviewing progress of the study and, if necessary, deciding on Protocol changes;
(iii) Review and approval of study publications and substudy proposals;
(iv) Reviewing new studies that may be of relevance.

Data Monitoring Committee
The independent Data Monitoring Committee is responsible for:

(i) Reviewing unblinded interim analyses according to the Protocol;
(ii) Advising the Steering Committee if, in their view, the randomised data provide evidence that may warrant a change in the protocol (e.g. modification or cessation of one or more of the treatment arms).

Central Coordinating Office (CCO)
The CCO is responsible for the overall coordination of the Study, including:

(i) Study planning and organisation of Steering Committee meetings;
(ii) Ensuring necessary regulatory and ethics committee approvals;
(iii) Development of Standard Operating Procedures and computer systems
(iv) Monitoring overall progress of the study;
(v) Provision of study materials to LCCs;
(vi) Monitoring and reporting safety information in line with the protocol and regulatory requirements;
(vii) Dealing with technical, medical and administrative queries from LCCs.

Local Clinical Centres (LCC)
The LCC lead investigator and LCC clinic staff are responsible for:

(i) Obtaining all relevant local permissions (assisted by the CCO)
(ii) All trial activities at the LCC, including appropriate training and supervision for clinical staff
(iii) Conducting trial procedures at the LCC in line with all relevant local policies and procedures;
(iv) Dealing with enquiries from participants and others.

8.5 Appendix 5: Organisational Details

STEERING COMMITTEE

(Major organisational and policy decisions, and scientific advice; blinded to treatment allocation)

Chief Investigator	Peter Horby
Deputy Chief Investigator	Martin Landray
Clinical Trial Unit Leads	Richard Haynes, Edmund Juszczak
Co-investigators	Kenneth Baillie (Scotland Lead), Thomas Jaki, Katie Jeffery, Wei Shen Lim, Alan Montgomery, Kathy Rowan
Other members	Saul Faust, Lucy Chappell, Marion Mafham

DATA MONITORING COMMITTEE

(Interim analyses and response to specific concerns)

Chair	Peter Sandercock
Members	Janet Darbyshire, David DeMets, Robert Fowler, David Lalloo, Ian Roberts, Janet Wittes
Statisticians (non-voting)	Jonathan Emberson, Natalie Staplin

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To enquire about the trial, contact the RECOVERY Central Coordinating Office

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Website: www.recoverytrial.net
(copies of this protocol and related forms and information can be downloaded)

To RANDOMISE a patient, visit:

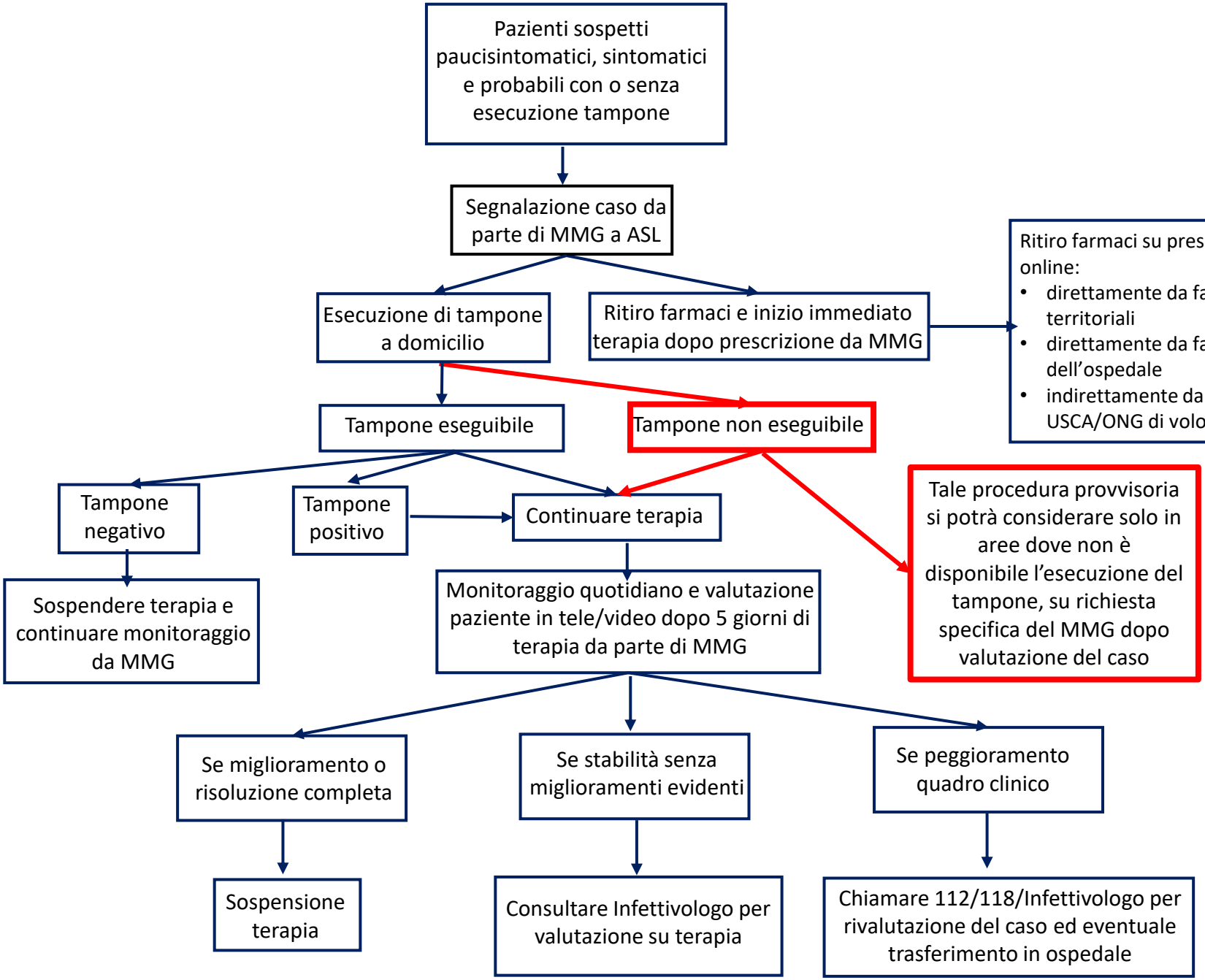
Website: www.recoverytrial.net

GESTIONE DOMICILIARE DELLA TERAPIA PRECOCE COVID-19 - Documento SIMIT condiviso da FIMMG e SIMG, Versione 27 Marzo 2020

ALLEGATO 3

Tipologia di paziente	Presentazione clinica	Monitoraggio	Trattamento farmacologico	Effetti collaterali dei farmaci e controindicazioni
Caso sospetto	Tosse secca, sintomi da raffreddamento	• Sorveglianza da MMG • Controllo temperatura corporea 2 volte al dì	Nessuno	Pazienti >65 anni con comorbidità : aumento rischio maggiori effetti collaterali dei farmaci [1]In associazione con Azitromicina aumenta rischio aritmie, in particolare in pz con sindrome QT lungo e anomalie della conduzione [2] Nausea, aumenta rischio aritmie, in particolare in pazienti con sindrome QT lungo e anomalie della conduzione
Caso sospetto paucisintomatico ((early/mild symptomatic)	Controllo temperatura corporea >37,5°C e < 38.6°C, tosse secca stizzosa, sintomi da raffreddamento senza dispnea	• Esecuzione tampone (se fattibile a domicilio) • Sorveglianza da MMG • Controllo temperatura corporea 2 volte al dì e atti respiratori 2 volte al dì	**Il trattamento prevede l'esecuzione di tampone. Solo in caso di impossibilità di esecuzione potrà comunque essere iniziato previa valutazione del caso da parte del MMG** • [1] **Idrossiclorochina**: 400 mg bid il primo giorno poi 200 mg bid dalla seconda alla decima giornata **oppure** • [1] **Clorochina** 500 mg bid il primo giorno poi 250 mg bid dalla seconda alla decima giornata **+** • [2] **Azitromicina** 500 mg per 5 giorni da assumere durante il pasto principale • **Aumentare idratazione** Antibiotici in alternativa ad Azitromicina per controindicazioni o allergie • **Cefixima** 400 mg per 5 giorni se controindicazioni ad Azitromicina • **Trimetoprim/sulfametossazolo** 160 mg/ 800 mg, 1cp 2 volte al per 5 giorni • in caso di controindicazioni a azitromicina ed allergia a cefixoral **Lo schema sopra indicato potrà essere modificato o integrato, anche con farmaci attualmente in uso, in base a nuove evidenze della letteratura scientifica.**	
Caso sospetto sintomatico e/o probabile	Controllo temperatura corporea ≥ 38.5°C, tosse secca stizzosa continua accompagnata o meno da dispnea	• Esecuzione tampone (se fattibile a domicilio) • Sorveglianza e valutazione rischio clinico da MMG (apposita scheda MMG) . • Valutazione clinica da MMG (apposita scheda MMG) • Controllo temperatura corporea 2 volte al dì • Controllo atti respiratori al minuto 4 volte al dì • Eseguire ECG per via telematica (in caso di impossibilità da remoto valutazione da parte del MMG dei fattori di rischio cardiovascolari se opportuno procedere a terapia) • Se in possesso di apparecchiatura portatile, valutazione 4 volte al dì della saturazione (se SpO2< 95 consultare MMG)		

GESTIONE DOMICILIARE DELLA TERAPIA PRECOCE COVID-19 - Documento SIMIT, Versione 27 Marzo 2020



Foglio illustrativo: informazioni per il paziente

Plaquenil 200 mg compresse rivestite
idrossiclorochina solfato

Legga attentamente questo foglio prima di prendere questo medicinale perché contiene importanti informazioni per lei.
- Conservi questo foglio. Potrebbe aver bisogno di leggerlo di nuovo.
- Se ha qualsiasi dubbio, si rivolga al medico o al farmacista.
- Questo medicinale è stato prescritto soltanto per lei. Non lo dia ad altre persone, anche se i sintomi della malattia sono uguali ai suoi, perché potrebbe essere pericoloso.
- Se si manifesta un qualsiasi effetto indesiderato, compresi quelli non elencati in questo foglio, si rivolga al medico o al farmacista. Vedere paragrafo 4.

Contenuto di questo foglio:

1. Che cos'è Plaquenil e a cosa serve

Plaquenil contiene idrossiclorochina solfato, che appartiene ad una classe di medicinali chiamati "antiparassitari-antireumatici".
Plaquenil è indicato per:
- adulti:
  - trattamento dell'artrite reumatoide in fase attiva e cronica, una malattia infiammatoria delle articolazioni;
  - trattamento del lupus eritematoso discoide e disseminato, una malattia del sistema di difesa dell'organismo caratterizzata da eruzioni in rilievo della pelle sensibili al sole, localizzate principalmente sul volto, braccia, torace e dorso
- bambini:
  - trattamento dell'artrite idiopatica giovanile (insieme ad altri medicinali), una malattia infiammatoria delle articolazioni;
  - trattamento del lupus sistemico eritematoso e discoide, una malattia del sistema di difesa dell'organismo caratterizzata da eruzioni della pelle sensibili al sole, infiammazione delle articolazioni con dolore e alterazioni del sangue e di organi e apparati quali il sistema nervoso, i reni, il cuore e i polmoni.

2. Cosa deve sapere prima di prendere Plaquenil

Non prenda Plaquenil

- se è allergico al principio attivo e ad altri medicinali simili a idrossiclorochina (4-aminochinolinici) o ad uno qualsiasi degli altri componenti di questo medicinale (elencati al paragrafo 6)
- se ha delle alterazioni di una parte dell'occhio chiamata retina e del campo visivo causate da medicinali simili a idrossiclorochina (4-aminochinolinici)
- se ha una malattia della retina dell'occhio chiamata maculopatia
- se il paziente è un bambino di età inferiore a 6 anni e con peso corporeo inferiore a 31 kg.

Avvertenze e precauzioni

Si rivolga al medico o al farmacista prima di prendere Plaquenil.

Deve usare Plaquenil con particolare cautela se:

- soffre di una malattia al fegato (insufficienza epatica) o ai reni (insufficienza renale) (il medico può ritenere necessario ridurre la dose di Plaquenil) o sta assumendo medicinali che agiscono su questi organi;
- ha dei disturbi allo stomaco e all'intestino (gastrointestinali), al sistema nervoso (neurologici) o al sangue (ematologici);
- è ipersensibile ad una sostanza detta "chinina";
- le è stata diagnosticata la mancanza di una sostanza presente nel sangue denominata "glucosio-6-fosfato deidrogenasi", o una malattia del sangue detta porfiria o una malattia della pelle chiamata psoriasi;
- sta prendendo medicinali che possono provocare infiammazioni della pelle (dermatiti);
- se lei soffre di prolungamento dell'intervallo QT congenito o acquisito (documentato con l'elettrocardiogramma).

Se non rileva un effettivo miglioramento dell'artrite reumatoide entro sei mesi di trattamento con Plaquenil, contatti il medico che valuterà se sospendere la terapia.

I pazienti in trattamento con Plaquenil possono ammalarsi al cuore (cardiomiopatie), con conseguente incapacità del cuore a pompare una quantità sufficiente di sangue all'organismo (scompenso cardiaco); alcuni di questi casi hanno portato alla morte.
Altri disturbi del cuore dovuti all'uso prolungato del medicinale possono essere: alterazioni del battito del cuore (blocco di branca/blocco atrio-ventricolare), o un aumento di una parte del cuore (ipertrofia biventricolare). Il medico la sottoporrà ad un controllo clinico del cuore e potrà decidere di sospendere il trattamento con Plaquenil.

Dopo trattamenti prolungati con dosi elevate di medicinali simili a idrossiclorochina (derivati chinolinici) sono stati segnalati, in rari casi, disturbi nervosi. È importante pertanto che lei si attenga alla dose che le

ha prescritto il medico. In alcuni pazienti che hanno ricevuto dosi elevate e prolungate di medicinali simili a idrossiclorochina (derivati 4-aminochinolinici) per il trattamento dell'artrite reumatoide e del lupus eritematoso, sono state osservate lesioni permanenti alla retina dell'occhio.
Se il medico prevede che lei debba seguire una terapia prolungata con Plaquenil, inizialmente le farà fare un esame approfondito dell'occhio (determinazione dell'acuità visiva, del campo visivo, della visione dei colori e l'esame del fundus). Questo esame verrà ripetuto almeno una volta all'anno.
La tossicità sulla retina dell'occhio è in gran parte in rapporto alla dose assunta del medicinale. Il rischio di danno alla retina è lieve alle dosi basse. Non superi la dose giornaliera raccomandata, perché può aumentare decisamente il rischio di tossicità alla retina.
Il medico le farà ripetere gli esami all'occhio più frequentemente se lei:

- assume un dosaggio giornaliero superiore a 6,5 mg/kg di peso ideale (calcolato come se lei fosse un soggetto magro)
- ha problemi ai reni (insufficienza renale);
- assume una dose totale di Plaquenil superiore a 200 g;
- è anziano;
- la sua vista è diminuita.

Se ha alterazioni della vista (alterazioni dell'acuità visiva, del campo visivo, della visione dei colori e della retina - quali alterazioni del pigmento, perdita del riflesso foveale - o qualsiasi disturbo visivo considerato anomalo dal medico), il suo medico le farà sospendere immediatamente il medicinale e la terrà sotto stretta osservazione per scoprire un'eventuale progressione di queste alterazioni. Le lesioni della retina (e i disturbi della vista) possono aggravarsi anche dopo la sospensione del trattamento con Plaquenil (vedere "Possibili effetti indesiderati").
Non si consiglia l'uso di Plaquenil con farmaci che possono provocare tossicità alla retina, per esempio il tamoxifene (un farmaco utilizzato contro i tumori).

Sono stati riportati casi molto rari di tendenze suicide in pazienti trattati con idrossiclorochina.
Con Plaquenil possono presentarsi dei disturbi, detti extrapiramidali, conseguenti ad alterazioni di una parte del sistema nervoso (vedere "Possibili effetti indesiderati").
Plaquenil provoca una grave diminuzione dei valori di zucchero nel sangue (ipoglicemia), inclusa la perdita di coscienza che può metterla in pericolo di vita sia che lei prenda o non prenda medicinali antidiabetici.
Se lei, durante il trattamento con idrossiclorochina presenta i disturbi dovuti ad un abbassamento degli zuccheri nel sangue (ipoglicemia) che le sono stati spiegati dal medico, verrà sottoposto a controlli del sangue e si potrebbe rendere necessaria una modifica della terapia.

Se lei sta seguendo una terapia a lungo termine con Plaquenil, il medico le farà eseguire periodicamente alcuni esami del sangue (esame

emocromocitometrico) e le sospenderà la somministrazione di Plaquenil in caso di risultati anomali. Il medico la sottoporrà anche ad un esame della funzionalità dei muscoli e controllerà la risposta muscolare ad alcuni stimoli nervosi (riflessi rotuleo ed achilleo). Qualora si manifesti debolezza ai muscoli (astenia) le verrà sospeso il trattamento con Plaquenil.

Alcuni dati ottenuti da esperimenti indicano un possibile rischio di mutazioni genetiche. Nell'uomo i dati sono insufficienti per poter escludere un aumento del rischio di cancro nei pazienti in trattamento a lungo termine.

Bambini e adolescenti
I bambini più piccoli sono particolarmente sensibili agli effetti tossici di Plaquenil e di medicinali simili (4-aminochinoline); se lei ha un bambino conservi Plaquenil fuori dalla sua portata e nel caso il bambino debba assumere il medicinale osservi scrupolosamente le indicazioni del medico.

Altri medicinali e Plaquenil
Informi il medico o il farmacista se sta assumendo, ha recentemente assunto o potrebbe assumere qualsiasi altro medicinale.

Gli effetti di Plaquenil possono essere influenzati o influenzare i seguenti medicinali.

- Digossina (un medicinale che serve per aumentare la forza di contrazione del cuore), poiché Plaquenil può aumentare i valori di digossina nel sangue. Il medico controllerà strettamente la quantità di digossina nel sangue se sta assumendo tale combinazione di medicinali;
- Insulina o farmaci antidiabetici (medicinali che riducono i valori degli zuccheri nel sangue) poiché Plaquenil può aumentare gli effetti di tali medicinali e il medico potrà decidere di abbassare le dosi dei medicinali contro il diabete;
- Fenilbutazone (usato per il dolore e l'infiammazione) o altri medicinali che abbiano tendenza a provocare malattie della pelle (dermatiti) e medicinali tossici per il fegato (epatotossici) poiché Plaquenil può aumentare questi effetti negativi;
- Plaquenil deve essere usato con attenzione se lei sta prendendo dei farmaci antiaritmici (utilizzati per il ritmo del cuore anomalo), farmaci antidepressivi triciclici (utilizzati per la depressione), farmaci antipsicotici (utilizzati per i disturbi psichiatrici), farmaci usati per le infezioni batteriche. L'alofantrina (usata contro la malaria) non deve essere usata con Plaquenil;
- Ciclosporina, poiché è stato segnalato un aumento dei valori nel sangue di questo medicinale quando assunto insieme a Plaquenil;
- Medicinali antimalarici che possono facilitare la comparsa di convulsioni (abbassare la soglia convulsiva), per esempio meflochina, poiché anche Plaquenil può dare convulsioni aumentando il rischio di questi eventi;
- Medicinali usati per l'epilessia, poichè potrebbero non funzionare se lei prende Plaquenil.

Clorochina, medicinale antimalarico, riduce l'attività di praziquantel (medicinale utilizzato per i parassiti). Un effetto simile può essere atteso anche per Plaquenil (che è simile alla clorochina).

Se Plaquenil viene associato ad agalsidasi (un farmaco per trattare una rara malattia presente alla nascita) l'azione di quest'ultimo medicinale potrebbe essere alterata.

Gravidanza e allattamento
Se è in corso una gravidanza, se sospetta o sta pianificando una gravidanza, o se sta allattando con latte materno chieda consiglio al medico o al farmacista prima di usare questo medicinale.

Gravidanza
L'assunzione di Plaquenil deve essere evitata in gravidanza: il medico potrebbe comunque prescriverlo in casi particolari, se lo ritiene assolutamente necessario.

Allattamento
Se lei sta allattando al seno deve fare particolare attenzione se è in trattamento con Plaquenil, poiché il medicinale è presente in piccole quantità nel latte materno, ma i bambini sono molto sensibili agli effetti tossici del medicinale. Le pazienti che assumono clorochina devono quindi consultare il medico prima di allattare al seno.

Guida di veicoli e utilizzo di macchinari
Durante il trattamento con Plaquenil, è sconsigliata la guida e l'uso di macchinari, in quanto idrossiclorochina può portare ad alterazioni della vista (influenza negativa dell'accomodazione visiva, annebbiamento della vista). In caso di assoluta necessità parli con il medico che potrà ridurre temporaneamente il dosaggio.

Plaquenil contiene lattosio
Se il medico le ha diagnosticato un'intolleranza ad alcuni zuccheri, lo contatti prima di prendere questo medicinale.

3. Come prendere Plaquenil

Prenda questo medicinale seguendo sempre esattamente le istruzioni del medico o del farmacista. Se ha dubbi consulti il medico o il farmacista.

Adulti

La dose raccomandata è:

- per l'artrite reumatoide**:**

  dose iniziale: da 400 a 600 mg al giorno (da 2 a 3 compresse rivestite) somministrate ai pasti o con un bicchiere di latte.

  In alcuni pazienti la comparsa di effetti indesiderati può richiedere la riduzione della dose iniziale. In seguito, dopo 5-10 giorni, la dose può

essere gradualmente aumentata fino a raggiungere quella ottimale, spesso senza che si ripresentino gli effetti indesiderati.

dose di mantenimento: quando si ottiene una buona risposta terapeutica, di solito tra le 4 e le 12 settimane, la dose viene ridotta a 200 - 400 mg (1 o 2 compresse rivestite) al giorno.

- per il lupus eritematoso:

dose media iniziale: 400 mg una o due volte al giorno.

Questa dose può essere continuata per diverse settimane o mesi in base alla sua risposta al medicinale.

dose di mantenimento: spesso sarà sufficiente una dose da 200 a 400 mg al giorno.

Il medicinale agisce accumulandosi nell'organismo e sono necessarie alcune settimane perché si manifestino i primi effetti benefici, mentre lievi disturbi possono presentarsi relativamente presto. Possono essere necessari diversi mesi di cura prima che si possano ottenere gli effetti massimi.
Il medico le sospenderà Plaquenil se le sue condizioni non miglioreranno in 6 mesi di terapia.

Il superamento delle dosi descritte per la terapia di mantenimento dell'artrite reumatoide e del lupus eritematoso causa una più alta incidenza di alterazioni della retina dell'occhio (retinopatia).

Con l'assunzione di Plaquenil, il medico può decidere di ridurre le dosi di altri medicinali che assume per il controllo della malattia (corticosteroidi e salicilati) o di sospenderli del tutto dopo che Plaquenil è stato assunto per parecchie settimane.
Se sta assumendo dei medicinali denominati corticosteroidi, il medico le ridurrà gradualmente la dose: attenersi scrupolosamente alle indicazioni del medico.

Bambini
Il medico adotterà la dose minima efficace di Plaquenil senza mai superare la dose di 6.5 mg. per chilo di peso, al giorno. Pertanto le compresse da 200 mg non sono adatte per l'utilizzo in bambini con un peso corporeo inferiore a 31 kg. Il medico fornirà comunque le indicazioni corrette anche per valutare il peso corretto (peso ideale) del bambino.

Se prende più Plaquenil di quanto deve
L'assunzione di una dose eccessiva di Plaquenil è particolarmente pericolosa nei bambini nei quali anche dosi basse (1 o 2 g) possono essere mortali.

Se ha ingerito accidentalmente una dose eccessiva di Plaquenil avverta immediatamente il medico o si rivolga al più vicino ospedale.

Plaquenil viene assorbito rapidamente e completamente dall'organismo dopo l'ingestione e in caso di dose eccessiva accidentale (più raramente anche a dosi normali se è un soggetto ipersensibile) entro 30 minuti possono manifestarsi sintomi tossici quali mal di testa, sonnolenza, disturbi alla vista, grave diminuzione della pressione del sangue (collasso cardiocircolatorio), convulsioni, diminuzione del potassio nel sangue (ipopotassiemia) e disturbi del battito del cuore (prolungamento dell'intervallo QT, torsioni di punta, tachicardia ventricolare, fibrillazione ventricolare e altre anomalie dell'elettrocardiogramma) che nei casi più gravi possono essere seguiti da improvviso arresto del respiro e del cuore, con rischio per la vita. E' necessario rivolgersi al medico o all'ospedale più vicino immediatamente poiché tali effetti possono comparire poco tempo dopo l'assunzione di una dose eccessiva.
Se ha qualsiasi dubbio sull'uso di Plaquenil, si rivolga al medico o al farmacista.

Se dimentica di prendere Plaquenil
Non prenda una dose doppia per compensare la dimenticanza della dose.

Se interrompe il trattamento con Plaquenil
Se ha qualsiasi dubbio sull'uso di questo medicinale, si rivolga al medico o al farmacista.
Se dovesse presentare una ricaduta dopo l'interruzione della terapia con Plaquenil, il medicinale può essere ripreso continuando con una somministrazione ad intervalli, se non esistono controindicazioni per i danni agli occhi.

4. Possibili effetti indesiderati
Come tutti i medicinali, anche questo medicinale può causare effetti indesiderati sebbene non tutte le persone li manifestino.

Sono stati osservati i seguenti effetti indesiderati:

Effetti indesiderati molto comuni (possono interessare più di una persona su 10):
- nausea
- dolori addominali

Questi sintomi si risolvono rapidamente riducendo la dose o interrompendo il trattamento.

Effetti indesiderati comuni (possono interessare fino ad 1 persona su 10)
- perdita di appetito (anoressia)
- instabilità dell'umore (labilità affettiva)
- mal di testa (cefalea)
- offuscamento della vista (dovuto a disturbi dell'accomodazione che dipendono dalla dose e sono quindi transitori)
- diarrea, vomito che si risolvono rapidamente riducendo la dose o interrompendo il trattamento
- disturbi della pelle (rash), prurito; tali effetti si risolvono rapidamente

interrompendo il trattamento.

Effetti indesiderati non comuni (possono interessare fino a 1 persona su 100):

- nervosismo
- capogiri
- alterazioni di una parte dell'occhio chiamata retina (retinopatia), con disturbi della vista (modifiche della pigmentazione e difetti del campo visivo). Nella sua forma iniziale, l'alterazione alla retina può guarire con l'interruzione della terapia, successivamente il rischio di peggioramento è possibile anche dopo la fine del trattamento. All'inizio la retinopatia può non dare disturbi o causare alcuni disturbi della vista (mancata visione centrale o vicino al centro dell'occhio, scotomi con anello paracentrale e pericentrale, scotomi temporali, alterata percezione del colore)
- vertigini, fischi o ronzii nelle orecchie (tinnito)
- alterati valori degli esami del sangue per la funzionalità del fegato
- disturbi della colorazione della pelle e delle mucose, imbiancamento dei capelli, perdita dei capelli; tali effetti si risolvono rapidamente interrompendo il trattamento
- alterazione della sensibilità e dei movimenti (disturbi senso-motori).

Effetti indesiderati con frequenza non nota (la frequenza non può essere definita sulla base dei dati disponibili)

- riduzione anche grave del numero delle cellule del sangue (depressione midollare, anemia, anemia aplastica, agranulocitosi, leucopenia, trombocitopenia)
- distruzione dei globuli rossi del sangue (emolisi nei soggetti con una malattia chiamata deficit di glucosio 6 fosfato deidrogenasi)
- orticaria
- rigonfiamento del volto, delle mucose delle bocca e della gola, con difficoltà a respirare (angioedema)
- restringimento dei bronchi con difficoltà a respirare (broncospasmo)
- bassi valori degli zuccheri nel sangue (ipoglicemia)
- peggioramento dell'alterazione di alcune sostanze che servono per la produzione del sangue (porfiria), che può portare a disturbi in numerosi organi, inclusa la pelle
- malattie mentali (psicosi)
- tendenze suicide
- irritabilità
- movimenti involontari degli occhi (nistagmo)
- perdita dell'udito
- convulsioni
- difficoltà di coordinamento muscolare (atassia)
- alterazioni a livello dell'occhio (maculopatie e degenerazione maculare) che possono non guarire
- disturbi del battito cardiaco (prolungamento del QT)
- alterazione del cuore (cardiomiopatia), che può portare a difficoltà

del suo funzionamento (scompenso cardiaco) e in alcuni casi alla morte, disturbi del battito del cuore (blocco di branca/blocco atrio-ventricolare) e aumento di volume di una parte del cuore (ipertrofia bi ventricolare). La sospensione del trattamento con Plaquenil può portare a guarigione
- gravissima malattia del fegato (insufficienza epatica fulminante)
- gravi reazioni bollose della pelle (compresi eritema multiforme, sindrome di Stevens-Johnsone necrolisi epidermica tossica, rash da medicinale con eosinofilia e sintomi sistemici - sindrome Dress, fotosensibilità, dermatite esfoliativa, esantema acuto pustoloso generalizzato (AGEP))
- diversi disturbi della pelle (urticarioidi, morbilliformi, lichenoidi, maculo papulari, porpora, eritema circinato centrifugo)
- aggravamento di una malattia della pelle detta psoriasi, accompagnato da febbre e aumento dei globuli bianchi (iperleucocitosi)
- danni ai muscoli (miopatia muscoloscheletrica o neuro miopatie) con debolezza e assottigliamento dei muscoli. Questi disturbi possono guarire dopo la sospensione del trattamento, ma la guarigione può richiedere molti mesi
- rallentamento della risposta muscolare ad alcuni stimoli e alterazioni del sistema nervoso (depressione dei riflessi tendinei e conduzione nervosa anomala)
- disturbi detti extrapiramidali, conseguenti ad alterazioni di una parte del sistema nervoso, che possono manifestarsi come contrazioni muscolari, movimenti involontari, tremori.

Altri effetti:
- perdita di peso
- stanchezza;
- una malattie della pelle detta psoriasi non sensibile alla luce
- alterazioni di una parte dell'occhio chiamata cornea, una membrana trasparente che ricopre la parte anteriore dell'occhio, che comprendono gonfiore (edema) e opacità, che possono essere senza sintomi o possono causare disturbi come aloni, offuscamento della vista o particolare sensibilità alla luce (fotofobia). Questi disturbi possono essere transitori o guariscono dopo l'interruzione del trattamento.

Segnalazione degli effetti indesiderati
Se si manifesta un qualsiasi effetto indesiderato, compresi quelli non elencati in questo foglio si rivolga al medico o al farmacista. Lei può inoltre segnalare gli effetti indesiderati direttamente tramite il sistema nazionale di segnalazione all'indirizzo www.agenziafarmaco.gov.it/content/come-segnalare-una-sospetta-reazione-avversa.
Segnalando gli effetti indesiderati lei può contribuire a fornire maggiori informazioni sulla sicurezza di questo medicinale.

5. Come conservare Plaquenil

Questo medicinale non richiede alcuna condizione particolare di conservazione.

Conservi questo medicinale fuori dalla vista e dalla portata dei bambini.

La data di scadenza si intende per il prodotto in confezionamento integro, correttamente conservato.
Non usi questo medicinale dopo la data di scadenza che è riportata sulla scatola dopo “Scad”. La data di scadenza si riferisce all’ultimo giorno di quel mese.

Non getti alcun medicinale nell’acqua di scarico e nei rifiuti domestici. Chieda al farmacista come eliminare i medicinali che non utilizza più. Questo aiuterà a proteggere l’ambiente.

6. Contenuto della confezione e altre informazioni

In una compressa:

- Il principio attivo è: idrossiclorochina solfato 200 mg
- Gli altri componenti sono: **lattosio monoidrato**, povidone, amido di mais, magnesio stearato, opadry OY-L-28900 (ipromellosa, macrogol 400, titanio diossido, lattosio monoidrato).

Descrizione dell’aspetto di Plaquenil e contenuto della confezione

Plaquenil si presenta in forma di compresse rivestite da 200 mg.
Una scatola contiene 30 compresse rivestite.

Titolare dell’Autorizzazione all’Immissione in Commercio e produttore

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Viale L. Bodio, 37/B- Milano
Produttore
SANOFI SYNTHELABO LIMITED-Edgefield Avenue – Fawdon-Newcastle-Upon-Tyne NE3 3TT (GB)

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Questo foglio illustrativo è stato aggiornato il

ALLEGATO 5

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7211615/

Vis J Emerg Med. 2020 Oct; 21: 100777.

Published online 2020 May 11. doi: 10.1016/j.visj.2020.100777

PMCID: PMC7211615

PMID: 32395638

Chloroquine/hydroxychloroquine overdose

Rita McKeever

During the COVID-19 pandemic, there have been many proposed medications that may be used to help treat this virus. One such medication is chloroquine/hydroxychloroquine Fig. 1 . Numerous institutions are currently studying these drugs to see their efficacy in the treatment of COVID-19. These notes are to help in guiding the diagnosis/management of overdoses of this medication.

Mechanism of action

• Block the synthesis of DNA and RNA and have some quinidine like cardiotoxicity
• Chloroquine is 2-3 times more toxic than hydroxychloroquine
• Sodium and potassium channel blockade are proposed mechanisms of cardiovascular collapse

Toxic dose

Therapeutic dose of chloroquine

• Prophylaxis for malaria - 500 mg/week for prophylaxis
• Treatment of malaria 2.5 gm over 2 days
• Reports of deaths in children after ingestion of 1-2 tabs.
• Lethal dose in adult ~30–50 mg/kg

Clinical Presentation

Symptom onset is rapid usually within 30 min, death within 1–3 hours usually from cardiac arrest [1, 2, 3].

Mild to moderate
• Dizziness, nausea/vomiting, abdominal pain, headache, visual/retinal disturbances, auditory disturbances, agitation, neuromuscular excitability.
• Can cause hemolysis in G6PD deficiency, rarely causes retinal damage, sensorineural deafness, hypoglycemia.

Severe
• Convulsions, coma, shock, respiratory/cardiac arrest [1, 2].

• Quinidine-like cardiotoxicity- Sino-atrial node arrest, depressed myocardial contractility, QRS and/or QTc prolongation, heart block, ventricular arrythmias, ST and T wave depression, u waves. Hypokalemia can occur and contribute to dysrhythmias [3].

Clinical criteria associated with fatal outcome [3]
• Ingestion of greater than 5 gm [2].
• Systolic BP <80 mm/Hg.
• Prolongation of QRS longer than 120 msec.
• Ventricular rhythm disturbances.
• Blood concentrations >8 mcg/ml.

Diagnosis/Treatment

• Early intubation/mechanical ventilation for significant ingestions/symptoms due to seizure risk/airway protection [3].
• Electrolytes, glucose, BUN, creatinine, EKG and tele-monitoring.
• Treatment of QRS prolongation with sodium bicarbonate is controversial. Be mindful that alkalinization can further exacerbate hypokalemia—before using sodium bicarbonate assess the full clinical picture specifically cardiac toxicity and degree of hypokalemia [3].
• K repletion for severe hypokalemia (usually due to intracellular shift not overall potassium deficit)—dose with caution and frequent potassium checks as redistribution of potassium may cause a rebound hyperkalemia and may worsen cardiotoxicity [3].
    • Hypokalemia correlates with severity of ingestion and occurs within a few hours of ingestion.
• Vasopressor support for hypotension not responsive to fluids.
    • Hypotension is multifactorial→
        • distributive from hydroxychloroquine/chloroquine induced vasodilation [2]
        • bradycardia from negative ionotropic effect [2]
        • cardiogenic effects from direct cardiotoxicity [2]
• Studies done with use of epinephrine (first line treatment)—0.25 mcg/kg/min and increase by 0.25 mcg/kg/min until adequate BP (~100 mmhg)—again monitor potassium as this can further cause intracellular shift [1, 2].
• High dose benzos—studies done with diazepam 2mg/kg IV over 30 min after intubation then 1-2 mg/kg/day [1, 2].
• Avoid type 1A anti-arrhythmics.
• Extracorporeal removal methods have not been shown to be useful—as hydroxychloroquine/chloroquine have large volume of distribution and significant protein binding [3].
• Questionable benefit from lipid emulsion therapy—there are a few case reports that have demonstrated improvement in patients that have overdosed on these medications [4].

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