Chloroquine/ hydroxychloroquine prevention of coronavirus disease (COVID-19) in the healthcare setting; a randomised, placebo-controlled prophylaxis study

UK Trial Overview v3.0, 1st July 2020

MORU Tropical Health Network

wellcome

UNIVERSITY OF OXFORD

UNIVERSITY OF OXFORD DIABETES TRIALS UNIT
The Oxford Centre for Diabetes, Endocrinology and Metabolism

brighton and sussex medical school

COPCOV Team

Co-Chief Investigator: Professor Sir Nicholas White
Chairman Wellcome Trust Southeast Asian Tropical Medicine Programmes & Consultant Physician
Mahidol Oxford Tropical Medicine Research Unit, Thailand

Co-Chief Investigator: Dr William Schilling
Research Physician & Infectious Diseases/ Microbiology Registrar
Mahidol Oxford Tropical Medicine Research Unit, Thailand

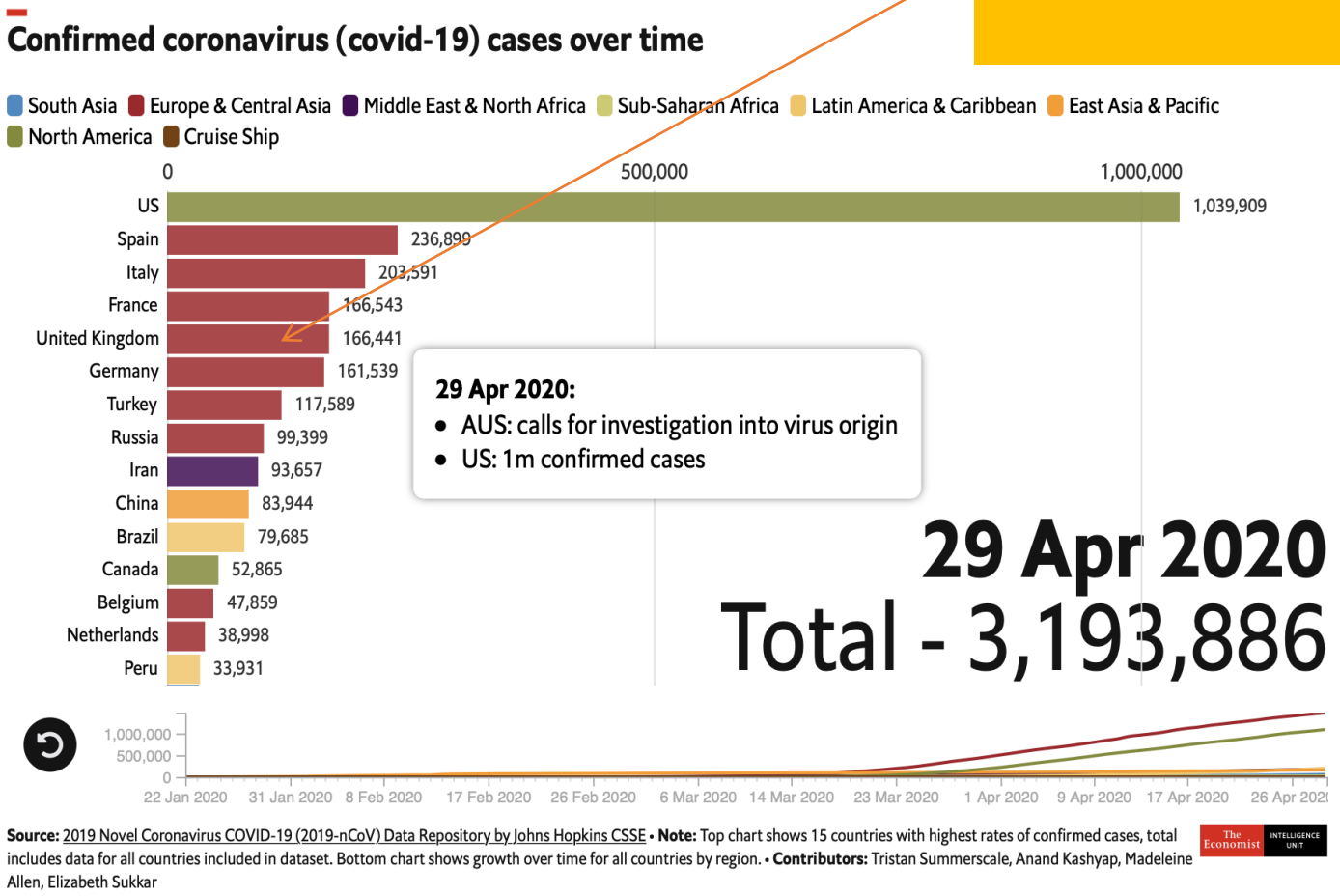
UK Chief Investigator: Professor Martin Llewelyn
Consultant in Infectious Diseases
Brighton and Sussex Medical School, UK

MORU: The MORU Tropical Health Network (https://www.tropmedres.ac/about) is responsible for the global management of the COPCOV trial.

DTU: The Diabetes Trials Unit (https://www.dtu.ox.ac.uk/AboutUs/) is a UKCRC registered trials unit and is responsible for the UK management of the COPCOV trial.

COVID-19 Status

166,000 cases as of 20 April - even if <<10% of cases diagnosed
vast majority of UK population remains at risk



Current interventions available

- Personal Protective Equipment
- Hand hygiene
- Social distancing

Vaccine 1-2 years away

Concern about lasting immunity

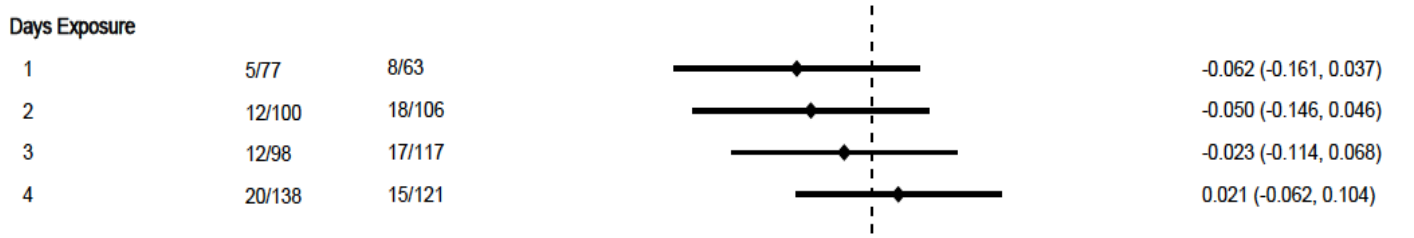
COPCOV

Scientific Rationale

- *In vitro* data in suggests (hydroxy)chloroquine has antiviral activity
- These are widely available drugs
- Extensive safety data in treatment of rheumatological disease
- Antiviral effect expected to be greater the earlier given in disease - ideally before infection
- Chemoprophylaxis being used in some counties - India, Egypt
- Chemoprophylactic efficacy and tolerability needs testing
- Healthcare workers - high-risk group
- Best design – randomized, double blind placebo-controlled trial

Recent controversies and evidence

- **May 22** - Study paused when large observational study of HCQ treatment reported this was associated with increased risk of death. **Subsequently retracted and the data appear to have been fabricated**
- RECOVERY Trial reported no benefit from HCQ **treatment** - but no safety concerns
- Boulware **post-exposure prophylaxis** trial reported small protective effect from HCQ (-17.5% relative risk) but not statistically significant. No safety concerns



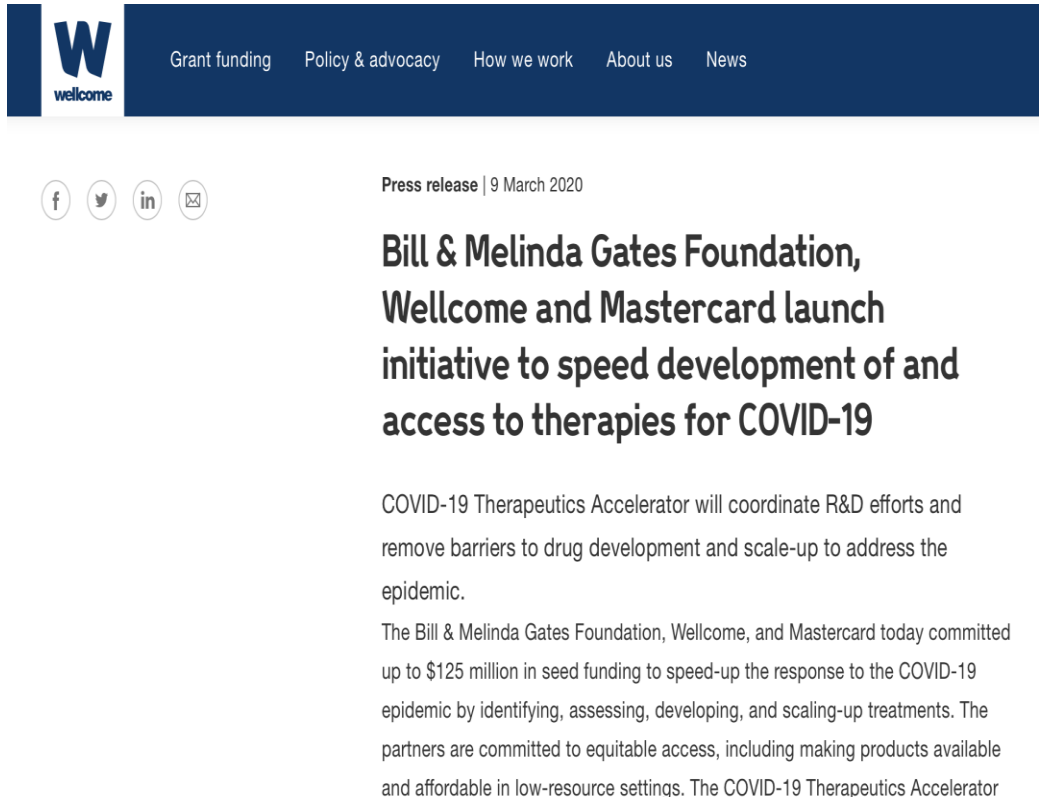
Point estimate relative risk reduction
Overall -17.5%
Day 1 -51%

Compatible with a clinically significant risk reduction if given as pre-exposure prophylaxis

- **June 26** MHRA approval and study re-opened
- **July 01** First site reactivated

Overview of COPCOV

- Double blinded, placebo controlled randomised controlled trial
- Recruiting healthcare workers and other staff in facilities managing COVID-19
- 40,000 Participants globally, 10,000 in UK
- Global study recruiting in SE Asia, Africa, Europe and North/South America
- Funded by COVID-19 Therapeutics Accelerator



Participating Sites

- UK sites will be set up at the Trust level and may run study clinics at multiple hospitals within their trust
- The number of hospitals within a trust is limited by the availability of IMP which is randomised in 200 kit blocks. Usually this will limit a trust to two hospitals
- The trial can be advertised at nearby healthcare facilities such as care homes and ambulance trusts
- Participants do not need to be employed by the participating trust to join this trial however, they must attend study visits at a participating trust

Recruitment Plan

- UK Sample size of 8,000-10,000 participants (not capped)
- 25 UK trusts will participate recruiting a target of 325-400 participants each (this can be discussed with the central trial team)
- There is no limit to individual site recruitment however please contact the central trial team to arrange additional IMP and supplies if intending to over-recruit
- The planned recruitment period is within 12 months of resuming enrolment. Individual participants will be on trial for a maximum of 5 months

Study Objectives

Primary Objective:

Determine if chloroquine/ hydroxychloroquine prophylaxis prevents symptomatic COVID-19 infection in healthcare workers and other staff working in facilities managing COVID-19

Secondary Objectives:

Determine if chloroquine/ hydroxychloroquine prophylaxis

- Attenuates COVID-19 severity
- Prevents asymptomatic COVID-19
- Prevents all cause symptomatic acute respiratory infections (ARIs)

Tertiary Objectives:

- Assesses health economic impact

Inclusion Criteria:

Not necessarily working at the site where they are recruited

- Healthcare workers and other staff working in a facility where there are cases of either proven, or suspected COVID-19

Defined very broadly including e.g. porters, catering staff, phlebotomists

- Agrees not to self-medicate with CQ/ HCQ or other potential antivirals
- Age ≥18, <70 (at consent)
- Not previously diagnosed with COVID-19

This means a laboratory (includes antibody as well as PCR test) diagnosis NOT suspected clinical

- Not currently symptomatic with a respiratory tract infection
- Has a smartphone: Android or iOS

Exclusion Criteria:

- Allergic to chloroquine / hydroxychloroquine / 4-aminoquinolines
- Contraindication e.g. known epilepsy, known creatinine clearance < 10 ml/min
- Already taking chloroquine / hydroxychloroquine / 4-aminoquinolines
- Taking certain concomitant medications
- Known retinal disease
- Inability to be followed up for the trial period
- Known prolonged QT syndrome (baseline ECG not needed)
- Known pregnancy or women who are actively trying to become pregnant
- Prior diagnosis of porphyria

Assessment of Eligibility

- Via a patient-facing online eligibility form
  - Gathers participant details and contact information
  - Checks details of inclusion and exclusion criteria and triages as either
    - Nurse-led local eligibility check
    - Doctor-led local eligibility check
    - excluded from the study
  - DTU forward information to local site staff to arrange enrolment D0 visit
- Site arranges D0 visit with participant

Procedures	Visits					
	Day 0 Enrolment	**Day 30 (-3 / +1)**	**Day 60 (-3 / +1)**	**Day 90 (-3 / +1)**	**Outcome follow-up if symptomatic (≤Day 150)**	**ARI Symptom onset[1]**
	1	**2**	**3**	**4**	**5**	***As needed during trial period***
Screening	X					
Eligibility assessment	X					
Informed consent	X					
Demographics	X					
Medical history	X					
Randomisation	X					
Set up mobile app	X					
Given thermometer	X					
Venous blood test	10ml			5ml	5ml, If not collected at D90	
Observed 1st dose of study medication	X					
Dispensation of study medication	X					
Compliance assessment		X	X	X		
DBS	X*	X	X	X*		
Adverse event assessments		X	X	X		
Questions about well-being, illness, COVID-19 diagnosis and clinical severity data	X	X	X	X	X	X
Nose and throat swab (+/- sputum)						X

[1] Can be repeated on multiple occasions if illness worsens or new ARI during trial period.

* This sample is expected to be obtained from the venous blood sample drawn at the same visit. If necessary direct finger prick may be performed.

Discontinuation of Study Drug

- Study medication should be discontinued if:
  - a participant is hospitalised with confirmed COVID-19 as a result of the infection (not for quarantine purposes)
  - a participant becomes pregnant during the trial
- If the participant's healthcare professional starts a treatment which is known to prolong the QT interval, while the participant is enrolled in the study, then an ECG should be performed by this professional and checked for QT prolongation
- Participants who discontinue study medication early will be encouraged to complete all other study assessments through Day 90

Study Withdrawal

All participants have the right to withdraw from the study at any time and can refuse the use of their data at any time up until the completion of the study (final follow-up of the final participant)

In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including:

- Ineligibility (either arising during the study or retrospectively as overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with treatment regimen or study requirements
- Withdrawal of Consent
- Loss to follow up (LTFU)

The reason for withdrawal should be documented in the EDC system

Definition of End of Study

In the UK, the end of the study will be after the completion of the final follow-up via medical records and organisations such as NHS digital - this will be 15 years after the last participant is randomised in the UK

Outcome/Endpoint Measures

- PCR proven SARS-CoV-2
- Seroconversion for SARS-CoV-2
- PCR proven respiratory virus(es)
- Severity score
- Quality of Life measures – EQ-5D-3L
- Days off work

Severity Score

Outpatient		
Group	Score/day	Definition
1	1	Feels unwell (reported on app but no specific symptoms)
2	5	Sore throat, runny nose, myalgia (not significantly limiting mobility), axillary temperature ≥ 37.5°C
3	25	Cough
4	250	Only able to leave chair/bed for short periods (~15mins) due to severe symptoms
5	500	Shortness of breath on exertion
6	1,000	Shortness of breath at rest

Severity Score

Inpatient: hospitalised on clinical grounds (not for control/isolation reasons)*		
Group	Score/day	Definition
7	10^4	Not requiring supplemental oxygen
8	10^5	SpO_2 < 94% (RA) or requiring** supplemental oxygen via face mask or nasal prongs
9	10^6	SpO_2 < 90% (RA) or requiring** supplemental high-flow oxygen or non-invasive ventilation
10	10^7	Requiring** intubation and mechanical ventilation
11	10^8	Ventilation and additional organ support (vasopressors, renal replacement therapy) or ECMO criteria met
12	10^{10}	Death

Efficacy Analysis

- Incidence rates calculated / arm
- N of COVID infections/person-time
- Ratio of CQ-HCQ to placebo
- Binomial negative to calculate 95% CIs
- If excludes 1, difference is significant
- Kaplan Meier – cumulative incidence
- Arms compared using log rank test

Other Analyses

- Adverse event rates - Chi-squared
- Severity score
  - Rank based mixed model stratified by site
- ANOVA F test to assess site differences
- QoL – descriptive analyses

Amendments

Substantial Amendment 01 – Approved 27th May 2020

- Addition of new participating sites and changes to PI

Substantial Amendment 02 – Approved 09th June 2020

- Broadening of inclusion criteria to include all staff at facilities managing COVID-19 not just those with direct care
- Pregnancy or intent to become pregnant added as an exclusion criteria, inclusion of information on pregnancy reporting
- Clarified that the trial will be advertised at neighboring healthcare facilities such as care homes and ambulance trusts
- Change to participating sites/PI

Substantial Amendment 03 – Approved 29th June 2020

- Age inclusion criteria amended to >=18, <70 (at time of consent)
- New exclusion criteria: prior diagnosis of porphyria
- Additional concomitant medications added
- Clarified that participants should halt taking study drug if diagnosed with COVID-19 and hospitalized
- Minor updates and clarifications throughout the protocol
- Change to participating sites/PI

Refer to amendment documents for full details.

Additional Information

Reference Documents:

- COPCOV UK Protocol
- COPCOV UK FAQ

Always refer to https://www.copcov.org/sites.html for correct version of documents

If you have any further questions please contact copcov@dtu.ox.ac.uk